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PELLAGRA IN THE AVERAGE POPULATION OF THE NORTHERN STATES*

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PELLAGRA is not confined to those two groups, alcoholic addicts and the Southern poor, whose dietary habits are notoriously bad and among whom the severe manifestations of the disease are especially common. Lesser deficiencies, not accompanied by florid dermatitis, diarrhea or dementia, are common in the average Northern population. They are the cause of important impairment of health.

Many have commented on the decreased vitamin content of the modern American diet, due to an increasing consumption of sugar and refined flour, with an ensuing decreased consumption of vitamin-containing foods. Studies by members of the U. S. Public Health Service[1] have not shown good pellagra-preventing values for many common foods other than meat, fowl and fish. The Bourquin-Sherman assay for vitamin B_2 is not a good indication of the pellagra-preventing value of foods. It is, rather, a measure of the riboflavin content.

There is considerable individual variation in the vitamin requirements of highly standardized rats.[2] Our observations indicate that some human subjects have unusual requirements without apparent organic cause. Many of our patients have had access to but have not selected an adequate diet. Many have had the onset of their deficiency symptoms during conditions which interfere with a normal intake or utilization of vitamins or which cause an increased requirement for them. These include pregnancy, organic gastrointestinal disease, severe or prolonged illnesses of various kinds and dietary restriction for therapeutic purposes. A vitamin deficiency, once acquired, may be prolonged by resultant anorexia. People with poor appetites tend to select high-carbohydrate foods of low vitamin content.

It is unfortunate that most of the descriptions of pellagra have emphasized the severe forms of the disease. The early symptoms and most of the lesser objective findings were recognized by European investigators and have been repeatedly described. For a thorough review of the literature up to 1919 reference may be made to the monograph of Harris.[3] He[4] and Goldberger,[5] among others, have appreciated that patients without the fully developed picture actually constitute a majority of pellagrins. This is in contradistinction to the old concept that the lesser symptoms occur during an incubation or a prodromal period, more or less prolonged. Harris[6] expresses the opinion that the great majority of pellagrins have suffered for years without ever progressing to the point of the classic condition.

The symptoms of pellagra are extremely varied and often multiple. Not corresponding to any localized organic disease, they commonly simulate some type of psychoneurosis. That the symptoms are functional is literally correct. They are the result of a disturbance in cellular metabolism. Because the correction of this disturbance of function is so easy, the recognition of its nature is of great importance. Removal of patients from the classification of psychoneurosis and the giving of a specific treatment promise to be one of the major accomplishments of medicine.

Although the symptomatology of pellagra is so varied, many of the symptoms are characteristic enough so that, occurring together without demonstrable organic cause, suspicion of their pellagrous etiology should be aroused. There are common signs other than the typical dermatitis which are almost entirely overlooked, and which may be of great value in suggesting the cause

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of an obscure set of symptoms. The classic dermatitis will not be discussed. It is seen only occasionally in our practice.

One of the characteristics of chronic pellagrous dermatitis is hyperkeratosis. Formation of callus occurs with slight provocation. One patient, who had been treated until his symptoms were well relieved and his chronic skin lesions had almost completely cleared, noted that a callus on the radial side of the proximal phalanx of the right index finger had disappeared. It had been present for years, and the only known reason for it had been the daily stropping of a razor blade, a practice which had not been discontinued.

These chronic lesions vary in appearance. Over the knees and instep they are usually wrinkled or creased in horizontal lines, giving a coarsely or finely serrated appearance. There may be fissures which rarely extend deep enough to appear raw at the base. The hyperkeratosis is occasionally nodular; it may have the roughness of sandpaper; there may be desquamation, varying from fine scales to large flakes, or the surface may be smooth and shiny. The hyperkeratotic skin commonly, but not always, shows pigmentation ranging from a light yellow, through brown to almost black. A vitamin C deficiency appears in some cases to have played a role in the pigmentation. These hyperkeratoses, as above noted, are an exaggerated response to irritation. They must be evaluated with regard to the degree of irritation to which the areas have been subjected. In many cases there has been no special irritation other than the friction of the clothing.

FIGURE 1. *Hyperkeratosis and Pigmentation over the Knees. This is unusually marked, with coarse scaling.*

Common sites for hyperkeratoses are over skeletal pressure points such as the knee (Fig. 1), elbow (Fig. 2), instep and front and back of the ankle. There are many descriptions of acute pellagrous dermatitis in such locations, and some[5, 7] have recognized that chronic lesions occur there without known preceding acute lesions. We have seen but a few acute erythemas over pressure points, and very few of our patients with chronic lesions have known of such an occurrence. Patients have frequently been aware of these areas of thickening and dryness of the skin for many years, and have commonly applied cold cream or oil to them.

Hyperkeratoses occur also over the soles of the feet (Fig. 3) and in that location have a significance that has not been appreciated. They are not necessarily conditioned by pressure, as they have been observed in patients who have been in bed for many months. They differ from ordinary calluses in being almost uniform over the soles

rather than limited to pressure areas, and in presenting varying degrees of cracking and scaling.

A fairly common type of hyperkeratosis is a more or less diffuse thickening of the skin over the fingers, disproportionate to the use which the hands have had. This is frequently most marked over the knuckles, especially the proximal phalangeal knuckles. The thickened skin may be smooth and white, or it may be fissured and rough and more or less pigmented.

Another common skin manifestation is an ichthyosis-like change, which has received little attention. Harris[8] quotes Calderini[9] and Gemma[10] as describing such a condition, and states that he

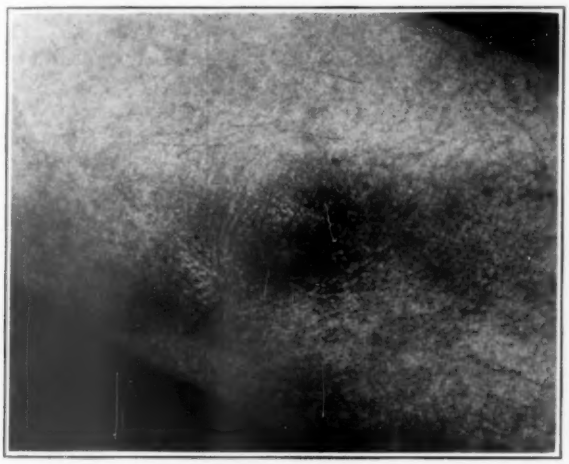

FIGURE 2. *Finely Roughened Hyperkeratosis over the Elbow.*

had seen well-marked ichthyosis in pellagrins. We have seen a few cases of marked scaling over the greater part of the body which had all the appearance of ichthyosis and which cleared following administration of the vitamin B complex. Much more commonly the changes are less marked, easily overlooked or attributed to chapping. They are not caused by chapping, due to environment alone, because the changes disappear after the administration of the vitamin B complex to ambulatory patients whose environment has not been changed. Nevertheless, environment is undoubtedly a factor. Ichthyosis is characteristically commoner and worse in the winter, and ichthyosis-like pellagrous scaling may be conditioned by exposure to cold or heat.

The usual site of ichthyosis-like changes is the anterolateral aspect of the calves (Fig. 4), less frequently the forearms. The edges of the plaques may or may not be loosened. They are usually separated by areas of normal-appearing skin. When the deficiency is severe, there may be marbled lines of erythema between the plaques. In a few cases the plaques are large and thick, simulating alligator skin.

A similar change is the occasional occurrence of an appearance of the skin over the legs which looks, by Stannus's[11] description, "as if a smooth layer of lacquer had been applied and then cracked mosaic-fashion." Sometimes the skin is uniformly smooth and shiny. Sometimes it may show a mosaic pattern of wrinkles only when it is relaxed ahead of traction in one direction. When severe there may be a yellow-brown pigmentation, and the skin over much of the body may resemble that of a well-roasted turkey.

A fine, branny desquamation has long been associated with cachectic diseases and with pellagra. It may be the result of poor hygiene, but if it persists or recurs after a few days of hospitalization it is significant. An irregular exfoliation of large, thin flakes may be seen, especially over the trunk.

Lesser changes than a red, sore and atrophic tongue may suggest a pellagrous stomatitis, although they are not always diagnostic. Occasionally the tongue is simply swollen, showing indentations from the teeth. It may appear normal except for redness with swelling of the fungiform papillae about the anterior edges and tip. At times the large, red fungiform papillae are seen against a background devoid of filiform papillae. There may be a heavy coat, usually not extending over the reddened tip and sides. This may desquamate overnight, leaving a beefy-red tongue. The desquamation may be irregular and progressive, giving the appearance of a "geographic tongue." Fresh deposits may then give areas with varying thickness of coat. Fissuring of the tongue has frequently been said to follow repeated attacks of pellagra. It has been fairly common in our chronic cases, but our observations do not afford proof of its etiology. Aphthous ulcers should always suggest the possibility of a pellagrous etiology.

The nervous and mental symptoms, short of dementia or psychosis, are exceedingly varied. Loss of energy, fatigability and weakness are usual complaints, and may constitute the presenting symptoms. Other symptoms or signs of deficiency may be absent, or may be recognized only after particular search for them. These symptoms require consideration of hypothyroidism and other conditions, such as chronic infection. A number of our patients had previously received thyroid medication, with doubtful benefit.

Vertigo is common, as is uncertainty of balance, and sometimes staggering without vertigo. Occasionally tinnitus is described. The head may feel dull, and difficulty in concentration may be

experienced. Cephalalgias vary from a sensation of fullness or pressure, localized or general, to boring or stabbing pains.

Paresthesias occur, such as numbness, burning or an itching or tingling sensation in the extremities and, less frequently, over the head.

A feeling of tenseness, irritability, mental depression and emotional instability are fairly common. Patients weep without cause. Insomnia is a frequent complaint. It has been known that tremors occur in pellagra. We have observed several patients with subjective sensations of internal tremors simulating those of hypoglycemia, except that they occurred without relation to the taking of food. They have been associated with minor skin changes and have been relieved after vitamin supplements.

Among gastrointestinal symptoms, constipation is perhaps the commonest and earliest. With a more severe deficiency, short spells of diarrhea may be interspersed with it. There may be peristaltic unrest and varying pains over the abdomen, which may become a severe colic. These symptoms are those of an irritable colon, and require differentiation from similar symptoms of intrinsic etiology. When there is mucus in the stools, mucous colitis may be simulated. Abdominal discomfort may also be simply a feeling of oversatiation after a small meal, one of weight in the epigastrium or a distressing sensation of bloating. The indigestion accompanying gall-bladder disease may be simulated by such discomfort occurring shortly after or during meals.

With a moderate deficiency, anorexia generally occurs. With a severe deficiency, food may be almost completely refused and vomiting may be serious. There may be a salty, bitter or "rotten" taste in the mouth. Occasionally there is increased salivation.

One of the most distinctive symptoms, usually denoting a fairly severe deficiency, is epigastric burning during or shortly after the ingestion of food, particularly acid food. With an esophagitis, foods may burn "all the way down." Occasionally the burning is continuous, causing a frequent desire for cold water. Otherwise the abdominal symptoms of pellagra may simulate so many other conditions that their evaluation must depend on

FIGURE 3. *Hyperkeratosis over the Soles.*

The lesions are unlike ordinary calluses: they are not limited to pressure points. There is characteristic cracking and desquamation.

association with skin lesions, some of the more distinctive nervous symptoms and a history of an inadequate diet.

From a large number of cases with signs and symptoms of a pellagrous type of deficiency, the following, uncomplicated by organic disease, are presented. They are representative of moderately severe deficiencies with more or less characteristic symptoms. They were all cases of referred patients who had had considerable previous medical attention.

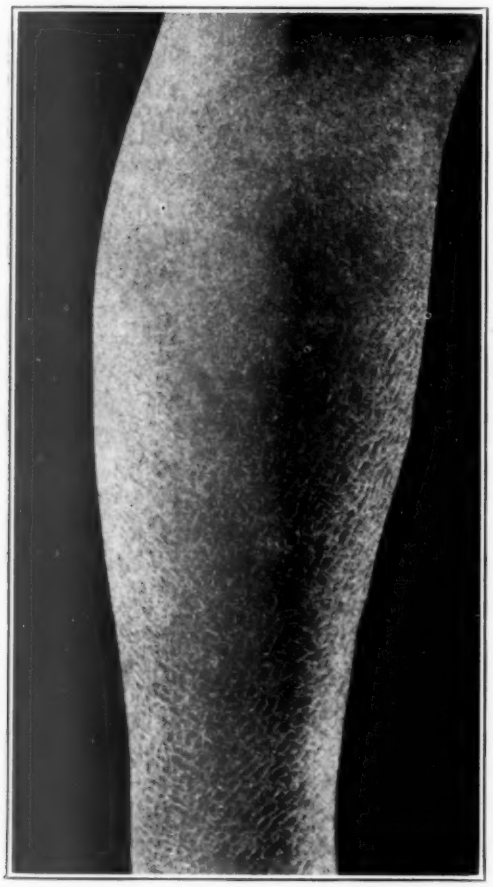

FIGURE 4. *Ichthyosis-like Scaling.*

This cleared after no change in regime other than the administration of vitamin B complex.

CASE 1. F. R., a 20-year-old housewife, had not been well since a pregnancy 18 months previously. After delivery she had had a complete paralysis of the legs for 2 weeks, followed by a slow recovery of function. For an unknown reason, — the urine and blood pressure were said to have been normal, — meat, fish and eggs had been withdrawn from the diet during the last 2 months of pregnancy. The presenting complaints were a feeling of exhaustion, marked, painless weakness of the legs after climbing one flight of stairs, middle-of-the-night insomnia, vertigo, uncertainty of balance so that she had to watch her feet while descending stairs, a burning sensation over the face and a feeling of fullness in the lower abdomen.

On physical examination the patient was obese. The skin over the elbows and knees was mildly thickened, and that over the insteps was moderately thickened and pigmented, with a fine serration and branny scaling. The tongue was reddened about its tip. Vibration sense of the ankles was moderately impaired.

The diet as described was not definitely inadequate. The patient was put on a 1500-calory reduction diet and given a supply of tablets of yeast and liver concentrate, supplemented with nicotinic acid. After 1 week she reported marked improvement in symptoms. The skin was not significantly changed. The tongue appeared normal. She still required an afternoon rest.

One month later, she felt completely well and was playing tennis for the first time in 2 years. The skin over the elbows and knees appeared normal. There were still slight thickening and pigmentation of the skin over the instep.

CASE 2. V. L., a 37-year-old housewife, had for many years had indigestion consisting of distention, belching and nausea. During her first pregnancy, 7 years before, she vomited almost daily and had one hematemesis. Since then she had had intermittent sharp pains in the epigastrium, extending over every part of the abdomen, and unrelieved by soda and occasional vomiting. During a second pregnancy 4 years later she had frequent emeses for 5 or 6 months and marked salivation.

On admission the patient was again pregnant, the last menstruation having occurred 2½ months previously. Emeses had become increasingly more frequent for 1 month. She had a burning pain in the epigastrium, to relieve which she drank cold water frequently. Previous constipation had increased and sharp pains over the abdomen were worse. The patient had become nervous and irritable, slept poorly and had occasional vertigo, twitching of the outer eyelids, headaches and a burning sensation over the upper trunk and head. Her weight had dropped from 260 to 230 pounds.

The dietary history was inconsistent. The patient had apparently had a somewhat inadequate high-carbohydrate diet for years, which became worse when she was pregnant.

Physical findings aside from an enlarged uterus were obesity, mild hyperkeratosis over the elbows, an ichthyosis-like scaling over the legs and markedly diminished vibration sense in the ankles. Two days after admission the patient developed overnight a brownish-red erythema over the knees (acute pellagrous dermatitis), which cleared in a few days without treatment.

X-ray examinations of the upper gastrointestinal tract, gall bladder and colon were normal. Urinalysis and the Kahn reaction were negative. The total serum protein was 6.6 gm. per 100 cc., with 3.3 gm. of albumin and 3.3 gm. of globulin. The blood ascorbic acid was 0.27 mg. per 100 cc. The urinary excretion of vitamin B_1 before and after a test dose was subnormal.

The patient was given 1.5 gm. of nicotinic acid in 5 days, followed by 40 mg. three times a day. At the same time she was given vitamin B_1, 5 mg. four times a day. After 8 days she reported much improvement. She had slept well for 2 nights, had only occasional mild burning sensations over the head or in the epigastrium, and had no more sharp pains in the abdomen. She was then given as a source of the whole vitamin B complex, liquor hepatis (*U.S.P. XI*), 15 cc. four times a day, supplemented by nicotinic acid, 20 mg. four times a day.

Two months later, having taken the medication irregularly, she reported feeling well most of the time, except for being somewhat fatigued. She had had a few spells of

nausea and burning in the epigastrium, which she thought were relieved by taking the medication more regularly. The ichthyosis-like scaling over the legs and hyperkeratosis over the elbows had disappeared except for a few loose flakes over the right elbow.

CASE 3. C. M., a 36-year-old housewife, had had a scaly skin since the age of 4, but had felt well until a pregnancy 9 years previously. Following delivery she lost 20 pounds in weight, which she never regained. She became fatigued easily and had an empty feeling in the midabdomen, which was relieved by the taking of food. Five years before she had been very weak and nervous and had had an intermittent diarrhea. Symptoms then abated somewhat but had been much worse for the last 7 months. The patient complained of nervousness, insomnia, choking sensations, frequent numbness of the hands, arms and ears, a "bad sensation" in the head and uncertainty of balance without true vertigo. She had a burning sensation in the epigastrium, increased by swallowing tomato or orange juice.

The diet consisted of low-vitamin foods except for one small serving of meat and one serving of carrots, peas or green beans a day.

Physical examination showed a moderate redness and enlargement of papillae over the tip of the tongue. The skin of the entire body was thickened and rough. Over the trunk there were large, thin, desquamating scales. Over the legs there was a marked ichthyosis-like scaling.

The patient was given powdered yeast, 45 gm. daily, supplemented with nicotinic acid, 240 mg. daily for 6 days, then 120 mg. daily.

Two weeks later she reported marked improvement in symptoms. She still became fatigued easily and had early morning insomnia. Three weeks later she was much stronger, slept well and had no abnormal sensations. At this time the skin was normal except for a few thin flakes over the trunk and some thickening of the skin over the legs, which was smooth and shiny, without scales.

In these three cases, symptoms arose during pregnancy. All the patients had chronic skin lesions. In Case 2 they were not marked, but an acute pellagrous erythema over the knees developed during observation. All the patients had characteristic nervous symptoms, including paresthesias, vertigo or uncertainty of balance and insomnia. In Cases 2 and 3 there was epigastric burning, aggravated by acid foods. Weakness and fatigue were pronounced in all the cases.

CASE 4. W. K., a 49-year-old man, a seed tester, had for 1½ years had intermittent, severe, colicky pains in the left upper quadrant, radiating to the left back, where there was also a burning sensation. During the physical examination the pains caused him to stiffen and wince. They were relieved following a gurgling in the left side of the abdomen. He had also had considerable constipation, weakness, spells of faintness and vertigo, dyspnea on moderate exertion and a weight loss of 28 pounds.

The diet had not been definitely inadequate before the present illness but had become so because eating induced the pains. The patient took two glassfuls of milk a day, less than one egg a day, meat rarely and green vegetables about once a week.

On physical examination there was moderate tenderness over the palpably spastic colon. There was no abdominal distention or visible peristalsis. The skin over the dorsum of the hands and forearms and over the knees was somewhat thickened, dry and rough, this condition being ascribed to his occupation. There was no x-ray evidence of intestinal obstruction.

Treatment was started with nicotinic acid, 60 mg. six times a day for 5 days, followed by 60 mg. three times a day, and thiamin chloride 5 mg. four times a day for 5 days, followed by 5 mg. daily.

At the end of 10 days the patient reported that he had had practically no abdominal pain after the 3rd day of medication. He felt stronger, had a good appetite and could eat foods that formerly precipitated pain — tomato juice among others. His only residual symptom was a burning sensation in the left lumbar region, present to a slight degree much of the time and aggravated by ingesting anything hot or a small amount of alcohol. There was no tenderness in the costovertebral angle. The patient was given a supply of tablets of yeast and liver concentrate. One month later he reported continued improvement. He had regained all his lost weight and normal energy.

In Case 4 the skin changes were not marked and the abdominal symptoms were strongly suggestive of intestinal obstruction, so that the weakness, vertigo and other symptoms were considered secondary until the absence of intestinal obstruction could be demonstrated.

CASE 5. R. F., a 41-year-old broker, began 3 months previous to admission to have a full feeling in the epigastrium immediately after eating and occasional sharp pains in various parts of the abdomen. Constipation of many years' duration had become worse and strong laxatives were being used. He had become nervous and tense, and had internal quivering sensations, especially when under strain. He had occasional spells of visual disturbance, sometimes blurring, sometimes "dancing vision" and sometimes blanking out of part of the visual field. Two months previously he had had a tight sensation about the heart, relieved by a week's rest in bed. Since then he had been more dyspneic than usual on climbing one flight of stairs.

Physical examination showed no remarkable findings except a branny scaling over the legs. An electrocardiogram was not abnormal.

The patient ate meat once or twice a day, but rarely had milk, eggs or green vegetables.

He was given a supply of tablets of yeast and liver concentrate. Three weeks later he reported marked improvement and had gained 5 pounds. The constipation and abdominal discomfort had been completely relieved. He felt less tense and had had no recent quivering sensation or visual disturbance. The skin of the legs was no longer scaly.

In Case 5 a branny scaling over the legs was the only objective evidence of deficiency. The visual disturbances were unusual. The relief of constipation was noted by the patient without any suggestion by the examiner.

Case 6. I. C., a 54-year-old housewife, was first seen in 1931, when her chief complaints were weakness and vertigo. She had not been well for many years, having a variety of symptoms including numbness and tingling of the hands and arms. Six years previously she had had a nervous breakdown, with the chief symptom extreme weakness, from which she had only partially recovered. She had had occasional vertigo for many years. Recent spells had been particularly severe, and since the last one there had been a feeling of insecurity of balance without vertigo.

Physical and laboratory findings gave no indication of organic disease. A neurological consultant reported the finding of glove hypalgesia in both arms and made the diagnosis of hysteria.

The patient was seen again 7 years later, when her chief complaints were weakness and fatigue. She continued to have mild spells of vertigo. Physical examination again revealed no significant findings except some thickening of the skin below the patellas.

The diet was of doubtful adequacy: no milk or eggs, one small serving of meat, one vegetable other than potato, and one salad, usually lettuce, each day. Because of this, the nature of the symptoms and the mild skin change, she was given a supply of tablets of yeast and liver concentrate. Two months later she reported complete well-being. Her diet was improved, and 8 months later she reported continued good health.

Case 7. B. M., a 41-year-old, single woman school teacher, had been below par since having bronchopneumonia 7 years previously. Her mother's health and finances had worried her, and for 3 months she had been "completely exhausted," nervous and irritable. For a month there had been short spells of vertigo and faintness. Recently there had been some insomnia.

She rarely ate meat or eggs, and the chief vitamin-containing foods in the diet were one glassful of milk and one green vegetable a day.

On physical examination the patient presented the appearance of marked fatigue, but there were no abnormal findings other than undernourishment.

She was given a supply of tablets of yeast and liver concentrate. Four months later she felt very well and had gained 12 pounds in weight. She had lost her appearance of fatigue.

The following December she reported having had a very good summer in the country, swimming and playing tennis every day. She had had fish daily and abundant vegetables. On returning to work her diet had become more deficient than ever, milk being usually omitted. For 6 weeks she had been tired and irritable, and had had occasional vertigo and an occasional drawing sensation in the abdomen. She was given dietary instruction and a supply of yeast and liver-concentrate tablets. Four months later she reported that she had felt very well through the winter.

Case 8. L. A., a 39-year-old, single woman school teacher, had been well except for chronic sinusitis and constipation until 1 year before, when she had had a "streptococcal" sore throat which kept her from work for 5 weeks. Following this attack she had been listless, weak and easily fatigued. Ten weeks previously she began to have burning pains in the epigastrium immediately after the ingestion of food, particularly acid foods, and sharp pains in various parts of the abdomen. For 2 months she had had occasional mild vertigo and three episodes of watery diarrhea lasting half a day each. Three years previously the basal metabolic rate had been reported to be —10 per cent. She had taken thyroid during the winter months for 2 years, and thought that it had somewhat helped her fatigability.

The physical examination and laboratory findings were normal. X-ray examinations of the chest, upper gastrointestinal tract, colon and gall bladder were normal. She had a normal gastric acidity.

According to a detailed history both before and after the x-ray examinations, the diet had been quite adequate. In addition, the patient had been taking a multiple-vitamin preparation with a low vitamin B_2 assay. Nevertheless, the abdominal pains, spells of diarrhea, fatigue and vertigo seemed so suggestive of pellagrous symptoms that she was given a trial of nicotinic acid, 60 mg. five times a day for 4 days and then 20 mg. three times a day.

Three weeks later she reported that on the 4th day of this medication she had noted an abrupt change and was able to eat very well without discomfort. Since then there had been an occasional half hour or hour of dull ache in the left upper abdomen, not related to meals, which was steadily decreasing. There had been no recurrence of diarrhea or vertigo. During the next month the abdominal pain completely disappeared and she felt well and strong. The patient then realized that she had not been healthy since her high-school days.

Case 9. D. W., a 56-year-old farmer, had not been well following a respiratory infection 1 year before. He had had dyspnea on exertion and fatigue so that he was unable to do more than occasional light chores. He had had abdominal distention, belching and epigastric burning after eating acid foods. He had had a period of "clumsiness" of the feet. He was irritable, and manifested character changes which made his family fear that he was becoming insane.

The diet included meat, eggs, two glassfuls of milk and fresh vegetables each day.

The chief physical findings were absence of vibratory sense in the legs, and skin changes. The tongue and mouth were normal. There were gross thickening and some fissuring of the skin of the fingers and hands. There were erythema, thickening and scaling over the elbows. Similar changes were more marked over the knees (Fig. 1), with light pigmentation about the border. There were patches of scaling over the lateral aspect of the lower third of the legs. The skin behind the ankles and over the toes was grossly hyperkeratotic. The soles were moderately thickened.

X-ray films of the chest showed a bilateral chronic (fibroid) pneumonitis, which did not change during the period of observation. There was normal gastric acidity.

The patient was given 60 gm. of brewer's yeast daily. Five weeks later he reported general improvement and a gain of 4 pounds. He was stronger but still unable to do much work. He had had but little abdominal distention and no pyrosis. There was a definite but not marked improvement in the skin lesions. He was then given nicotinic acid, 400 mg. daily for 1 week and 120 mg. daily thereafter, with 20 gm. of brewer's yeast daily.

Two months later he reported further symptomatic improvement. He had been doing all his farm work for 3 weeks. The abdominal symptoms had disappeared and the mental outlook was improved. The skin was normal except for some pigmentation over the knees and slight scaling over the lateral aspect of the leg.

Cases 7 and 8 had symptoms without objective evidence of deficiency. In Case 9 the symptoms followed a respiratory infection, of which a chronic

fibroid pneumonitis was apparently the residuum. In Case 7 the patient dated her ill-health to an attack of bronchopneumonia seven years previously. In Case 9 the skin lesions with their erythematous bases showed evidence of acute as well as chronic activity—a rare occurrence with us. Cases 8 and 9 gave histories of adequate diets. It will be desirable to confirm by chemical studies that an occasional individual can have a pellagrous vitamin deficiency while taking a normal diet. Neither of these patients had gastric anacidity.

Discussion

It is apparent that pellagra presents no uniform clinical picture. It may cause important and sometimes serious symptoms without the classic dermatitis and sometimes without the lesser chronic skin lesions. Such cases will be overlooked unless the various symptoms and the lesser objective manifestations of pellagra are kept in mind. The gastrointestinal symptoms, except pyrosis, are seldom distinctive. However, their association with skin changes and with nervous symptoms like paresthesias, vertigo, some cephalalgias, depression and emotional instability may be significant. Occasionally, symptoms may be suggestive enough to warrant a trial of vitamin supplements despite a history of a seemingly adequate diet and the absence of objective signs of deficiency, as in Case 8.

The possibility that a pellagrous type of deficiency may be a common cause of symptoms brings to discussion several considerations. We have become reluctant to accept many diagnoses of psychoneurosis without taking a detailed dietary history and searching for objective signs of deficiency. It is recognized that a psychoneurosis may be a predisposing background for the development of a nutritional deficiency. In such cases, relief of superadded symptoms should be worth while. It need hardly be said that organic disease should be excluded before a diagnosis of deficiency is accepted without reservation. A deficiency state may develop secondary to organic disease. On the other hand, there are many cases in which extensive investigation is not of immediate life-saving importance. In these the psychotherapeutic and reassurance value of such investigations may not warrant their expense before making a test of vitamin therapy.

It may also be said that many patients who present chronic skin and tongue changes admit no symptoms that seem ascribable to a deficiency. (It has been noted above that the significance of hyperkeratoses must be evaluated with due regard to the amount of irritation to which the skin has been submitted, and that ichthyosis-like scaling is especially common in cold weather.) In such cases the diet should be improved, but vitamin supplements do not seem necessarily indicated unless the patient is about to undergo a serious operation. In that event, they would seem indicated in order to assure an optimum cellular metabolism.

Recent observations have clarified considerably the problem of the treatment of pellagra. Symptoms are contributed by deficiency in various factors of the vitamin B complex, but nicotinic acid has proved to be of outstanding importance. It is present in relatively small amounts in natural materials used as therapeutic sources of the vitamin B complex. A good yeast contains about 0.5 mg. per gram, and a good liver extract for oral use contains about 1.0 mg. per gram. Therefore, for practical therapeutic and economic reasons, synthetic nicotinic acid is recommended as the backbone of the treatment. Curative doses of nicotinic acid ranging from about 100 to 500 mg. or more per day[12, 13] have been reported. The limiting factor in dosage is the flushing reaction caused by nicotinic acid. This reaction is a pharmacologic effect of the acid while it is accumulated in the blood stream awaiting synthesis into its amide and the higher compounds that are the effective vitamins.[14] Such reactions do not occur following the administration of nicotinic acid amide. We have found doses of 60 mg. six times a day satisfactory in producing prompt results without causing uncomfortable reactions in most patients until an adequate total dosage has been approached. When significant reactions occur regularly, the size of the dose, and later its frequency, may be reduced until the patient is taking from 80 to 160 mg. per day in three or four doses. In some patients not under close observation it may be desirable to start treatment with frequent 40-mg. doses.

For the rest of the vitamin B complex, natural sources are recommended, at least for the present. The observations of Sebrell and Butler[15] indicate that a minimal curative dose of riboflavin for cheilosis or angular stomatitis is 0.025 mg. per kilogram of body weight per day. This dosage, then, should give reasonably prompt results in any lesser riboflavin deficiency. Using the smaller reported figures for riboflavin equivalence to a Sherman unit of vitamin B_2, this dosage may conservatively be considered to be afforded by 600 to 700 such units daily for an average-sized individual. Doses of most natural products with this amount of vitamin B_2 contain amounts of vitamin B_1 which are adequate unless a definite polyneuritis indicates additional supplements. Little is known concerning human requirements for other factors of the complex. That they are of importance is

suggested by some experiences, such as that of a patient with a psychosis, dermatitis and glossitis who became oriented and no longer maniacal after large doses of nicotinic acid, remained stationary for two weeks during the consecutive administration of thiamin and riboflavin, and became normal after taking the whole vitamin B complex.

The above figures represent curative doses for cases with severe deficiencies. Smaller doses may be sufficient for some individuals who are not severely depleted. Inadequate doses, however, will produce disappointing results.

With doses like the above there should be obtained pronounced improvement in gastrointestinal and nervous symptoms in less than a week. For complete relief it will be necessary, in a few cases, to continue for some time the administration of larger amounts of nicotinic acid than the follow-up doses suggested above. Chronic skin lesions sometimes clear completely within two or three weeks, sometimes only after many weeks, and occasionally they show only partial improvement after long continuation of the whole vitamin B complex in larger doses than suggested above.

After the deficiency has been relieved, it is desirable to improve the diet so that further vitamin supplements will not be needed. In some pathologic conditions this may not be possible. It seems that occasionally an apparently normal individual needs vitamin supplements in addition to a presumably normal diet.

The question of nomenclature for the types of cases under discussion arises. The terms "pellagra sine pellagra" and "subclinical pellagra" do not seem appropriate for deficiency states that are the cause of clinical disability, although the classic dermatitis is lacking. These terms imply an obscurity that does not stimulate an alertness to detect the condition. Certainly the cases with chronic skin lesions herein described justify the descriptive name "pellagra." It seems justified to extend the use of the name to those cases, lacking any skin lesions, which have the same symptoms and which are relieved by the same vitamin supplements. There are many precedents covering similar situations in medicine. More important than the name, however, is the recognition that such cases do occur, and not infrequently.

Summary

Evidence has been presented of the frequent occurrence in the northern part of the United States, among the better as well as among the poorer economic classes, of important disabilities due to a pellagrous type of deficiency. The symptoms are reviewed, and the frequently occurring but commonly overlooked objective manifestations of the condition are described.

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DIRECT VISUALIZATION OF THE PLACENTA BY SOFT-TISSUE ROENTGENOGRAPHY*

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BALTIMORE

IT HAS long been a rule that every gravida who has vaginal bleeding during the last trimester of pregnancy should be examined vaginally. Since the main purpose of the examination is to establish or rule out the diagnosis of placenta previa, the procedure entails insertion of the finger through the cervix and palpation of the area immediately surrounding the internal os. The dangers of such an examination are obvious, namely, precipitation of fresh hemorrhage, introduction of infection and initiation of premature labor. Realizing the disadvantages of vaginal examination in these cases, various investigators have attempted to localize the placental site by other methods.

More than a century ago, when Kegaradec[1] first described the uterine souffle, he believed that it was of value in determining the location of the placenta. This sound, of course, is the result of the passage of blood through dilated uterine vessels, and while such vessels are naturally more numerous beneath the placental site, the findings are not dependable. Steele,[2] however, is of the opinion that auscultation of the abdomen after the sixth month of pregnancy will indicate the approximate location of the placenta in at least 75 per cent of cases. Rectal examination has also been employed, but this not only carries with it the danger of precipitating hemorrhage, but is often inconclusive.

Erhardt[3–5] and Katsuya[6] were the first to localize the placenta with the aid of roentgen rays. They injected Thorotrast (thorium dioxide solution) intravenously into experimental animals. This method was suggested to them by slightly earlier work done to visualize the liver and spleen in human subjects and in animals. These organs produce a shadow in the roentgenogram, since the radiopaque thorium is stored in the reticuloendothelial cells of the liver and spleen and remains in the maternal blood sinuses of the placenta for some hours. Shute and Davis[7] repeated this work with other thorium preparations, and made exhaustive pathological studies of the organs of mothers and their offspring. Thorium has been found to be extremely toxic for many vital organs, and has a narrow margin of safety. Especially large doses are required for visualization of the liver and spleen, and even with these, immature placentas are often poorly visualized or cast no shadows at all. The maximum intensity of the placental shadow may not appear until hours after the injection of thorium, thus unduly prolonging the diagnosis of placenta previa in cases of vaginal bleeding. There is a tendency toward induction of labor and some reason to suspect permanent sterility as a result. The placenta seems to be an effective barrier to the passage of thorium preparations, for the drug has never been demonstrated in the fetal tissues and the babies appear normal. Thorium itself is radio-active, so that the drug stored in maternal organs for months is quite undesirable. Furthermore, Schmidt[8] warns against the possible danger of further x-ray examination of patients who still have a radio-active drug retained in their tissues. In the light of these studies, it seems difficult to understand how anyone could suggest the clinical use of such a dangerous substance.

Amniography, an aid to localization of the human placenta by means of x-ray photography, was introduced in 1932 by Campbell, Miller, Menees and Holly.[9] An aqueous solution of strontium iodide was injected into the amniotic cavity by way of a lumbar-puncture needle inserted through the anterior abdominal and uterine walls. The gestational sac cast a shadow on the x-ray plate and the placenta appeared as a filling defect. Several investigators have employed this method, and various radiopaque dyes have been used: Uroselectan (Kerr and Mackay,[10] Burke[11]); barium sulfate (Burke); Neoskiodan (Cornell and Case[12]); and Perabrodil (Burke). There have been serious objections to the use of this method, and it has not been widely employed. The chief objection is the inherent danger to the abdominal contents of blindly inserting the needle through the abdominal and uterine walls, although there have been no published reports of injury to the intestines. A second objection is the possibility of trauma to the fetus, placenta or umbilical cord. In each case reported by Cornell and Case the placenta was pierced, but in the light of Snow and Powell's[13] observations this is not a surprise, for in each case they chose for the site

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of entrance the side of the maternal abdomen opposite the fetal back. Again, they found that in 2 of their 6 cases the umbilical cord had been punctured. A third objection to this method is the great possibility of induction of labor. Burke found labor setting in so regularly after the injection of Uroselectan that he purposely attempted induction of labor by this means in 27 cases, failing in only 1, a case of hydramnios.

Hewitt[14] attempted to inject Lipiodol directly into the placenta implanted over the lower uterine segment, by selecting various sites in the wall of the vagina through which to insert the needle. If the placenta was successfully injected with small quantities of the dye, the latter were expected to appear on the roentgenogram as small globules. If the placenta was located in the fundus, the injected Lipiodol was expected to gravitate away from the sites of injection and appear as streaks on the x-ray plates. In actual practice, however, these results were not observed with any degree of certainty, and the method carries all the inherent dangers enumerated for amniography.

Indirect placentography, accomplished by studying the size and shape of the space between the posterosuperior wall of the urinary bladder, previously injected with a solution of sodium iodide, and the lower margin of the presenting fetal head, was introduced by Ude, Weum, Urner and Robbins.[15] Moderately good results have been reported in selected cases by McDowell,[16] Hall, Currin and Lynch,[17] McIver,[18] Friedman and Macdonald,[19] Priest,[20] Jablonski and Meisels,[21] Wells,[22] Beck and Light[23] and Williams.[24] The normal cystocephalic space in late pregnancy measures not more than 1 cm. on the roentgenogram. It appears larger whenever the placenta or any other

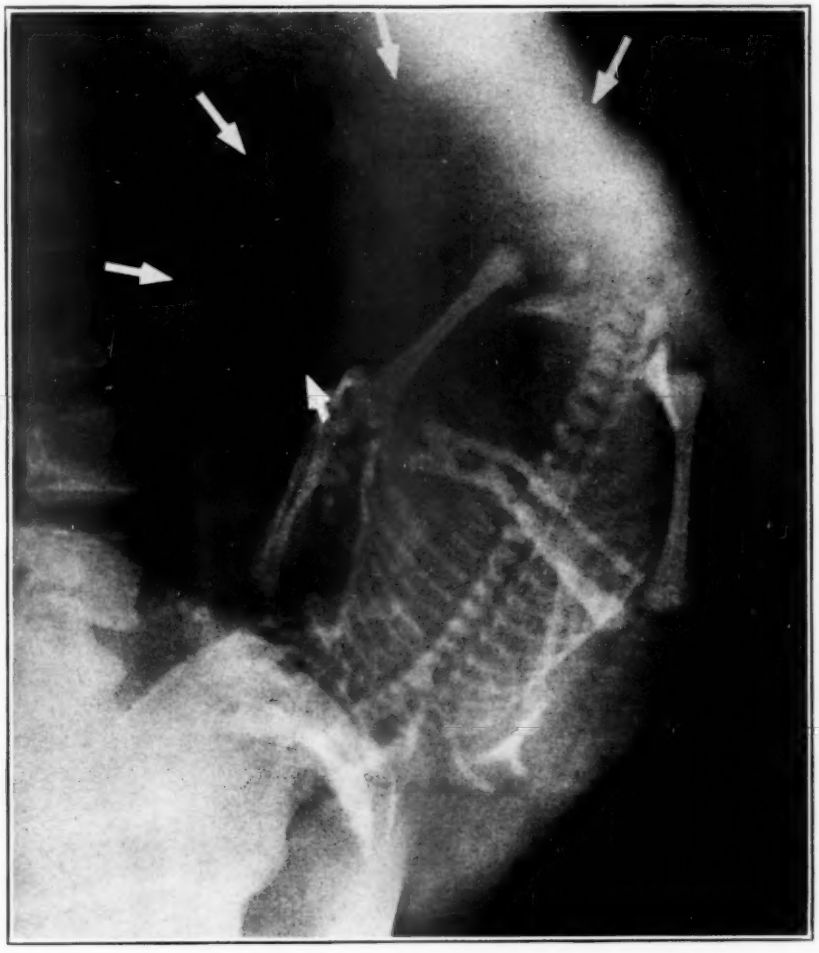

FIGURE 1.

Roentgenogram of a young primipara (E. P.) with a normal pregnancy, taken at term. The placenta is implanted over the posterior uterine wall, well up in the fundus.

soft-tissue tumor is interposed between the bladder and the presenting fetal head. In general this method has not been found adaptable to other than vertex positions. For example, Beck and Light were forced to discard the procedure in 21 per cent of the 90 bleeding cases examined by them in the last trimester, because the fetus presented by the breech or transversely. This must be considered a definite disadvantage, since any method of localization of the placenta finds its greatest usefulness in cases of suspected placenta previa and breech and transverse presentations are notably commoner in this obstetric complication than in normal pregnancy. Furthermore, Jablonski and Meisels and Beck and Light have shown that a placenta attached to the posterior wall of the lower uterine segment may be erroneously diagnosed as normal by cystography. This method requires the minimum amount of experience in roentgenologic technic, but apparently a certain amount of experience is highly essential to a correct interpretation of the roentgenograms. This is particularly true when the findings are not strictly consistent with normal ones or with those typical of placenta previa, as in cases where the pregnancy has not advanced well into the last trimester.

FIGURE 2.

Roentgenogram from a moderately obese primipara (R. G.) who had slight vaginal bleeding in the thirty-fifth week of gestation, beginning with premature spontaneous rupture of the membranes. This and a small fetus, with the head floating above the pelvic inlet, aroused suspicion of placenta previa. The soft-tissue roentgenogram revealed that the placenta was implanted over the anterior wall of the fundus and ruled out placenta previa. The patient was discharged, but readmitted two days later; spontaneous delivery of a small term-size child was effected.

From time to time, various roentgenologists have reported visualization of the placenta in conventional roentgenograms. Baumann[25] showed one of these; Staveley,[26] however, states that the placenta is not normally visible, but may show

calcified patches which might be useful in the diagnosis of placenta previa. Occasionally one sees the placenta in roentgenograms taken for purposes of pelvimetry, but always independent of calcification.

The introduction of soft-tissue roentgenography has opened a promising field in all branches of medicine, for by its use one may visualize the soft tissues with the same detail as one does the osseous structures in conventional roentgenograms. The technic employed is essentially the same as that used in ordinary roentgenography. This method has been developed in general medicine, particularly by Carty,[27, 28] while Snow and his coworkers[13, 29, 30] have introduced it into obstetrics.

In 1934, Snow and Powell[13] reported a study of 60 pregnant women by means of soft-tissue roentgenography. In the majority of cases the placenta was located by observing the site at which the uterine wall appeared to be unusually thickened. On the roentgenograms it measured about 7 cm. at the point of greatest thickness and tapered off toward the periphery. In practically all cases the ventral surface of the fetus faced the placenta, and in none was the fetal back directed toward it. Very often a knee, an elbow, a foot or a hand of the fetus caused a pressure defect in the placenta. Snow and Powell believed that visualization of the placenta very low in the uterus, or failure to visualize it, would aid greatly in establishing the diagnosis of placenta previa. Snow[29] later reported the successful diagnosis of several advanced extrauterine pregnancies. This was made possible by noting the absence of the uterine wall

FIGURE 3.

Roentgenogram from a secundipara (C. G.) with moderately profuse vaginal bleeding, beginning ten days before the estimated date of confinement. The roentgenogram shows the placenta implanted over the lower anterior wall of the fundus. Labor was induced, and the hemorrhage controlled by a large Voorhees bag. A clinical diagnosis of low implantation of the placenta was made at delivery (version and extraction).

around the gestational sac. More recently Snow and Rosensohn[30] have pointed out the value of locating the placenta in patients who have previously been delivered by cesarean section. In the event of anterior attachment of the placenta in a subsequent pregnancy they recommend another cesarean section, in order to avoid the added risk of rupture of the uterus. In cases of suspected placenta previa they also employ aerocystograms, in order to study the cystocephalic space.

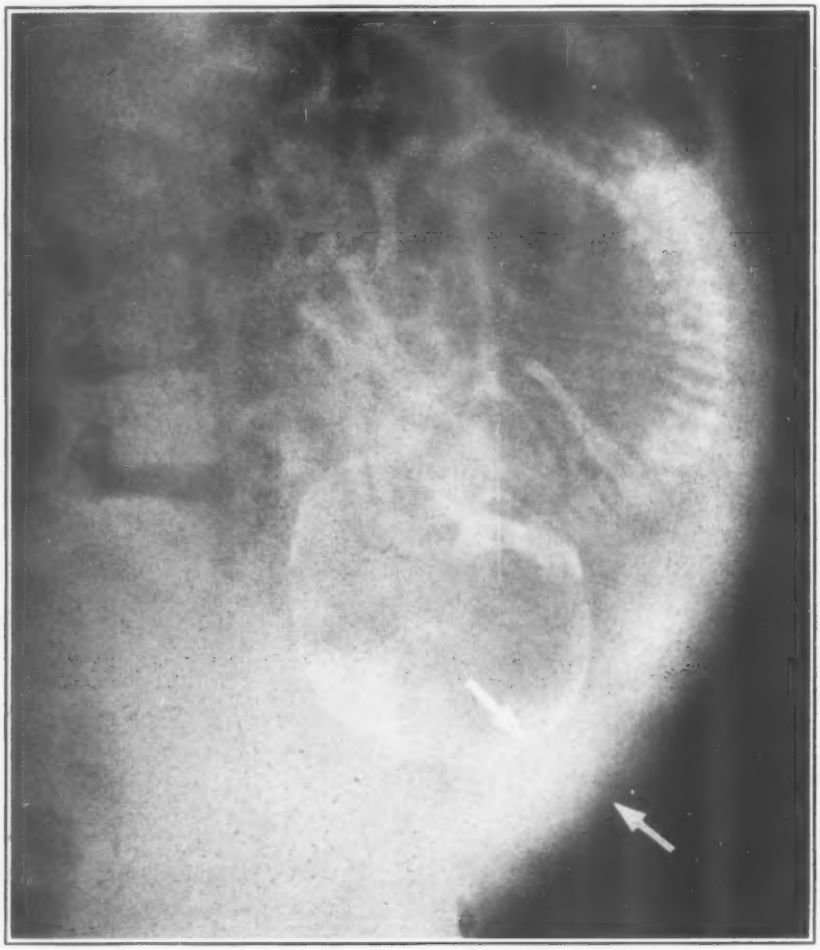

FIGURE 4.

Roentgenogram from a secundipara (I. C.), taken in the thirty-second week of pregnancy on account of painless vaginal bleeding following intercourse. The roentgenogram shows the placenta extending only a short distance up the anterior wall of the lower uterine segment. A diagnosis of central placenta previa was ventured and confirmed by vaginal examination and at cesarean section.

During the last eighteen months we have employed soft-tissue roentgenography in examining almost 200 pregnant women; roughly one fourth of these patients were x-rayed on account of bleeding in the last trimester. The placenta was clearly visualized in approximately 90 per cent of the cases. In the remainder there were certain definite deterring factors which rendered visualization difficult or impossible. The placenta cannot be visualized in cases of hydramnios, and only occasionally in cases of multiple pregnancy. Unusual obesity of the mother renders visualization more difficult. Prematurity has not offered any great obstacles, and although with immature fetuses the chances of visualization are definitely reduced, we have been able to demonstrate the placenta clearly in a pregnancy advanced to only the twenty-fourth week. The position of the fetus in no way deters good visualization. When the placenta is implanted over the lower uterine segment, its lower margin is usually not perceived. However, if one reasons that the normal placenta at or near term covers approximately one fourth of the surface area of the uterine wall, as has

been demonstrated by Torpin,[31] the probable type of placenta previa may be diagnosed with reasonable accuracy. In a small percentage of these patients the location of the placental site was checked at cesarean section or by vaginal examination, and in no case was the roentgenological diagnosis found to be erroneous. Moreover, the future course of the pregnancy in all cases was in conformity with the roentgenological diagnosis. Two illustrative x-ray plates are shown in Figures 1 and 2.

FIGURE 5.

Roentgenogram from a primipara (N. P.), taken in the thirty-eighth week of pregnancy because of suspected moderate hydramnios. The roentgenogram shows a large fetus in vertex position, with a calcified placenta attached to the whole of the anterior wall of the fundus.

Since we adopted this technic the number of vaginal examinations made to determine the cause of bleeding has been greatly reduced. After being x-rayed, many patients are discharged to carry on the pregnancy and to be delivered normally at or near term. A single lateral roentgenogram is usually sufficient. We have not found the anteroposterior view of any particular aid. Earlier writers have shown that the placenta is usually attached to the relatively flat anterior or posterior uterine wall, and Torpin,[31] with a new method of studying placentation, has recently confirmed this. He found that the placenta seldom extends over the dividing line between the anterior and posterior walls, either laterally or over the apex of the fundus; and that when it does, it is apt to be a placenta bipartita, succenturiata or spuria. For this reason the placenta is almost invariably located on a lateral roentgenogram.

While the most important use of soft-tissue roentgenography in obstetrics is in cases of suspected placenta previa, there are other applications of the technic which offer possibilities.

We agree with Snow and Rosensohn[80] that the preoperative knowledge of the location of the placenta, regardless of the type of contemplated op-

eration, is of distinct value. Thus, before performing a cesarean section on a patient with an anteriorly located placenta, one might wish to take additional precautionary measures in the way of facilities for transfusion. One might conceivably care to choose between a classical and a low cervical cesarean incision, depending on whether the anteriorly implanted placenta were situated in the lower uterine segment or in the fundus. Again, exact knowledge of the site of attachment before the insertion of bougies for induction of labor will guide one in selecting the anterior or posterior wall of the uterine cavity for this purpose, and thus lessen the possibility of separation of the placenta.

Before the advent of soft-tissue roentgenography, there was no method of determining the condition of the old cesarean scar in subsequent pregnancies. By means of visualizing the comparative thickness of the anterior uterine wall and the smoothness of its outline, which is made possible by the soft-tissue technic, it may be possible to ascertain the soundness of the old scar. To date we have seen 2 cases in which the anterior uterine wall in a pregnancy subsequent to a classical cesarean section appeared to be irregularly thinned, and it was believed unsafe to allow these patients to go through normal labor. This thinning was subsequently confirmed at operation. Further in-

FIGURE 6.

Roentgenogram from a thirty-eight-year-old multipara (A. A.) with an ectopic pregnancy who was admitted two months after her calculated date of confinement and four months after the cessation of fetal movements. She had had slight vaginal bleeding just after fetal death, but none thereafter, and she observed that the abdomen had grown progressively smaller. Soft-tissue roentgenograms were obtained, but not interpreted before laparotomy. Note the thin-walled gestational sac, the dead fetus and the non-pregnant uterus over the lower anterior wall of the product of conception.

vestigation will be necessary before a definite statement on this possibility can be made.

Specific information on the x-ray technic to be employed in obtaining soft-tissue roentgenograms is not described here in detail, for it must vary with the x-ray equipment at one's disposal. Some of the new grades of contrast films seem to be eminently suitable for this work. Contrary to the general impression that costly high-powered machines are necessary, good soft-tissue work can be done with a simple portable outfit. The technic employed in our x-ray department is one of high voltage and low exposure time. We use a constant milliampere-second ratio, the factor being made up of 50 milliamperes and 4 seconds. The voltage (peak) is varied between 65 and 85 kilovolts, depending on the obesity of the patient. No special roentgen-tube equipment and no filters are used. Any intensifying screen may be employed. Carty[27] stresses the importance of development of the films by sight, and states that they cannot be developed successfully by a strict time-and-temperature method. A certain amount of experience in the use of x-ray apparatus is necessary, but this is acquired by trial and error and with only a moderate expenditure of time and material.

The technic of viewing soft-tissue plates is quite important. This is certainly true of lateral views, as we have thus far been unsuccessful in obtaining lateral roentgenograms of even density. The intensity of different areas varies so widely that strong illumination, as with a spotlight, can be used to marked advantage in the region of the anterior abdominal wall. Since the exposure is made to produce the maximum soft-tissue detail in the region of the posterior uterine wall, the anterior uterine wall, which represents much less thickness of tissue, is overexposed. The reproductions (Figs. 1–6) have been made from translucencies (direct reductions from roentgenograms), which in turn were made possible by photographic shadowing or dodging in order to produce photographs of essentially even intensity. They represent normal cases and those of probable placenta previa, as well as certain other obstetric complications. These would seem to afford convincing evidence of the value of soft-tissue roentgenography in the field of obstetrics, particularly abnormal obstetrics, regardless of whether such abnormalities be actual or only suspected.

Summary

Various methods of visualization of the placenta are discussed.

The placenta can be visualized by soft-tissue roentgenography in a high percentage of cases.

This is a valuable aid in cases of suspected placenta previa, and usually obviates the necessity of vaginal examination.

It is possible that the application of this technic to other obstetric conditions will also be of value.

We are indebted to Mr. J. C. Fletcher, chief technician of the Department of Roentgenology, for his efforts in developing the soft-tissue technic in our laboratory, and for his aid in obtaining photographic reproductions of the roentgenograms.

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SUBDURAL HEMORRHAGE IN PATIENTS WITH MENTAL DISEASE*

A Statistical Study

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FOR twenty years the Department of Mental Health of the Commonwealth of Massachusetts has maintained a pathologist and a laboratory. The duties of this physician have been to investigate the sudden and unexpected deaths occurring in state mental hospitals, to give assistance to the resident pathologists in the several state hospitals and to perform the duties of resident pathologist in hospitals which lack such officers. From the beginning of the service in July, 1914, to July, 1934, 3100 autopsies were performed, for the most part by the same operator, Dr. Myrtelle M. Canavan. The protocols of these cases have been investigated in order to determine how often subdural bleeding occurred among patients who died while confined to mental hospitals. The majority of the patients in the series were residents of Massachusetts, and although some racial differences occur among them, they were for the most part of similar stock. An additional factor which favored uniformity was the similarity of standards for diagnosis and treatment in the hospitals from which the material was obtained, all of which are under the administration and supervision of the Department of Mental Health.

There is considerable range in the medical vocabulary of terms describing the lesion dealt with in this study. It is therefore advisable to indicate some of the commoner terms that have been used in the past to describe intracranial bleeding of subdural location. Those most commonly encountered are subdural hemorrhage, subdural hematoma, hematoma of the dura mater, hygroma, subdural blood cyst, meningeal blood tumor and pachymeningitis hemorrhagica interna. Additional terms are listed and their sources given by Robertson.[1] For the purpose of this study, the term "subdural hemorrhage" is used according to the definition of Dr. Canavan: "Extravascular blood in any condition or amount between the dura and arachnoid." Cases in both acute and chronic stages of this condition are included in this series, ranging in extent from the presence of fluid blood and blood clots, with or without membrane formation, to a thin, brown membrane attached to the under surface of the dura. However, we cannot state definitely the size of the lesions, since only a few of the autopsies were done by one of us (A. M. A.). Two cases were found in which the end result was calcification, and there were a few bilateral hematomas.

Of 3100 autopsy protocols examined, there was evidence in 245 cases (7.9 per cent) of subdural hemorrhage of varying degree and in varying locations. In 117 cases death was due chiefly to disease of the nervous system (Fig. 1). In 87 cases

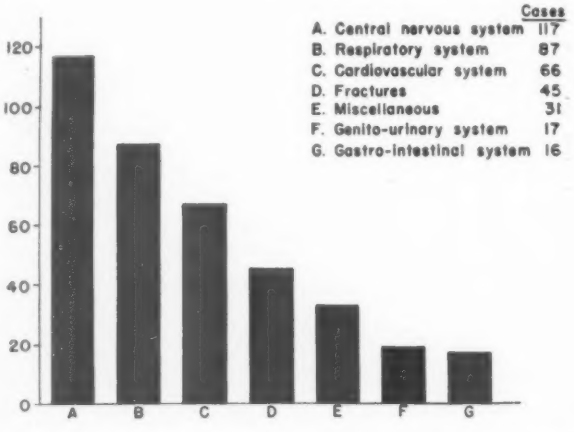

FIGURE 1. *Causes of Death Classified According to the Body Systems in 245 Patients with Subdural Hemorrhage.*

disease of the respiratory system was the primary cause. In 66 cases there was evidence of severe cardiovascular disease, and in 45 death was believed to be caused by complications of fractures, chiefly of the skull. In the few remaining cases death was due to genitourinary and gastrointestinal conditions and a few miscellaneous causes.

In the group of patients who died of neurologic disorders, the conditions most frequently observed were intracranial tumor, meningitis, hydrocephalus, edema of the brain, laceration of the brain, dementia paralytica and tabes dorsalis. In 35 of these cases subdural hemorrhage was the primary cause of death. Forty-five additional cases showed

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other types of intracranial bleeding, that is, extradural, subarachnoid and intracerebral hemorrhages. There were 35 cases of dementia paralytica.

Deaths due to pulmonary disease were next in order of frequency. Bronchopneumonia caused death in 44 cases and lobar pneumonia in 19. Pulmonary tuberculosis was the primary cause in 21 cases. Pulmonary edema, empyema, gangrene and emboli were occasionally reported. Diseases of the heart and the circulatory system were considered to be the chief cause of death in 66 cases.

Trauma was frequent in this series, and fractures were extremely numerous. There were 29 skull fractures and 18 fractures of other bones. In the group of patients with subdural hemorrhage the incidence of fractures was 19.1 per cent.

Three cases of suicide are included. They were due respectively to a wound in the head, hanging, and slashing of the throat. Relatively few persons died of primary disease of the genitourinary system; in the 17 cases so diagnosed, chronic interstitial nephritis occurred most frequently. Pyelonephritis, cystitis and ruptured bladder were other conditions of importance. The smallest number of deaths were due to gastrointestinal disease.

The weight and height of the patient at the time of death were not always recorded, so that an estimate of the general state of nutrition cannot be exact. However, it has been shown[2] that the general body condition and nutrition of patients with mental disease, as evidenced by the weights of specific organs, are somewhat inferior to those of patients who have been in general hospitals for only a short time before death.

All the patients in this series were insane with the exception of 2 who were mentally deficient.

When classified according to psychiatric diagnosis, the highest percentage (15.0) was found in the group of cases diagnosed as "psychosis with other brain or nervous disease."* Generally the exact neurological disease was unspecified in the autopsy report. In many cases which show a large subdural hemorrhage at autopsy, the association of a psychosis with vague neurologic signs gives a clinical picture suggestive of syphilitic or alcoholic origin or of brain tumor. It was exceptional to find subdural hemorrhage listed as an etiologic factor in patients receiving the above psychiatric diagnosis.

A survey of the literature indicates the general agreement among the students of this condition that subdural bleeding is a commoner postmortem finding among psychotic patients than it is among general hospital patients. Wiglesworth[3] found 54 cases (8.4 per cent) in 637 autopsies and Lewis[4] found 81 cases (7.9 per cent) in 1565 autopsies. In our series, there were 345 cases (7.9 per cent) in 3100 autopsies. At the Boston City Hospital, a general hospital, Munro[5] observed 215 subdural hemorrhages among 1203 cases of head injury selected for neurosurgical treatment. These patients were admitted over a six-year period and all had suffered trauma. There are few data available that give the incidence of subdural hemorrhage among general hospital patients, and available autopsy data in general hospitals do not report the incidence, since in most general hospitals a postmortem examination of the skull contents is not regularly made unless the clinical examination suggests some lesion in the brain. In view of this fact, reliable statements in regard to the incidence of subdural hemorrhage in nonpsychotic patients are rare. In our 3100 autopsies, it is important to note that in almost every case the skull was opened and the contents examined.

In considering why subdural hemorrhages are found more commonly at autopsy among psychotic patients than among general medical patients, Robertson[1] stated in 1900: "They occur most commonly in the insane of a somewhat advanced age, and . . . are found in the great majority of instances in patients in whom the mental disease has been of long standing. The form of insanity that furnishes the largest proportion of cases is general paralysis." Althaus[6] expressed similar views in 1878 when, speaking of the occurrence of subdural hemorrhages among mentally sound patients, he stated that they occurred "in the *old, decrepit, worn-out, intemperate*," and were "not infrequently associated with low forms of pleuropneumonia, pneumothorax, pleurisy, pericarditis, emphysema, rheumatic fever, delirium tremens, leukaemia, pernicious anaemia, scurvy, haemophilia and the various forms of Bright's disease of the kidneys." He added, "It has occasionally become developed in the course of whooping cough from excessive venous congestion brought on by severe paroxysms of coughing, and injury to the head may also lead to it." Subdural hemorrhage has been reported to occur in association with typhus fever, chronic alcoholism, infantile scurvy and tuberculosis.

Our incidence of subdural hemorrhage of 7.9 per cent may appear excessive, but several factors warrant consideration. Many patients had psychoses definitely associated with organic intracranial disease, such as cerebral arteriosclerosis and dementia paralytica. Trauma may have been commoner in this group of patients than among nonpsychotic persons.

*Organic, but not specifically classified (Table 2).

Among the 245 patients with subdural hemorrhage, 148 (60.4 per cent) were men and 97 (39.6 per cent) women, a ratio of 1.5:1 (Table 1).

TABLE 1. *Distribution of Cases of Subdural Hematoma According to Age and Sex.*

YEARS	MALES	FEMALES	TOTAL
0–10	1	0	1
11–20	3	0	3
21–30	5	2	7
31–40	14	10	24
41–50	27	18	45
51–60	33	11	44
61–70	30	29	59
71–80	18	19	37
81–90	17	6	23
91–100	0	2	2
Totals	148	97	245

Brain[7] claims a greater preponderance of men over women, in the proportion of approximately 5:1. The findings of Leary[8] — chiefly medicolegal — more nearly approximate the proportion found in our series; he reports 50 cases of subdural bleeding in which there were 34 men and 16 women, a ratio of approximately 2:1.

In our series cases of subdural hemorrhage were found among patients who died in all decades of life (Table 1, Fig. 2). The greatest number (59)

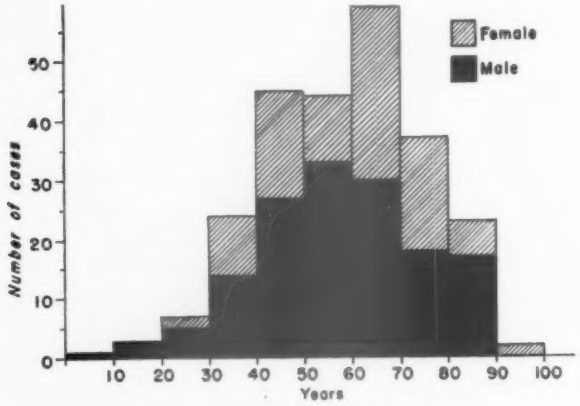

FIGURE 2. *Sex Distribution and Age at Death in 245 Patients with Subdural Hemorrhage.*

were found in patients who died between sixty and seventy years of age. One case was that of a boy who died before his tenth year. Two women died between ninety and one hundred. There were almost twice as many patients between forty and fifty at death as there were between thirty and forty.

The largest number of male patients were between fifty and sixty years old at death. There was a steady increase by decades until the sixty-year mark was reached; after that there were fewer cases. There were no female patients with subdural bleeding who died between one and twenty years of age. There was an irregular distribution by decades after that age until the seventh was reached. In this decade the largest number of cases occurred. There was a rapid decrease in number of cases in the eighth, ninth and tenth decades. An interesting frequency of occurrence was noted in the fifth decade (18 cases), whereas there were relatively few cases in the fourth (10) and the sixth (11).

The range of ages at death appeared to be approximately the same for both sexes. The personality of male patients in respect to aggressiveness and activity may be considered as a factor in producing subdural hemorrhage. Among women, a more protected situation and lesser activity may tend to limit its incidence. The factors of alcoholism, syphilis and trauma may contribute to the difference in sex incidence among male patients, and these factors may be more important than among women. Subdural hemorrhage among women may occur as a result of changes more dependent on cerebral vascular conditions than is the case among men.

When classified according to psychosis, 79 patients were found to have had mental disorders associated with old age, such as cerebral arteriosclerosis and senile conditions (Table 2). The

TABLE 2. *Psychiatric Diagnoses in All Autopsied Cases and in Those with Subdural Hemorrhage.*

PSYCHIATRIC DIAGNOSIS	NO. OF CASES AUTOPSIED	CASES WITH SUBDURAL HEMORRHAGE	
		NO.	INCIDENCE PER 1000 CASES
Psychosis with other brain and nervous diseases	101	16	159
Epileptic psychosis	178	22	124
Dementia paralytica	338	35	104
Psychosis with cerebral arteriosclerosis	417	43	103
Senile psychosis	413	36	87
Alcoholic psychosis	192	16	83
Dementia praecox	576	35	61
Psychosis with mental deficiency	234	11	47
Manic-depressive psychosis	171	8	47
Undiagnosed psychosis	116	3	26
Psychosis with somatic disease	158	3	19

frequent finding of subdural hemorrhage among these patients may be related to the presence of other findings such as marked brain atrophy, with a consequent increased size of the subdural and subarachnoid spaces. The brain atrophy that occurs in elderly patients may cause a strain on unsheathed pial veins after the brain and dura separate. The emaciation, malnutrition, weakness and unsteady gait of elderly persons may render them more liable to trauma.* Further research is indicated in order to place these poten-

*Vitamin C levels in the blood plasma have been shown to be significantly low in a group of patients suffering from senile psychoses and psychoses associated with cerebral arteriosclerosis.[9]

tial factors in a true causal-consequential sequence.

Next in size after the group of patients with senile psychoses are those with dementia praecox and dementia paralytica (35 each). The pathological findings in these psychoses when uncomplicated are so dissimilar that an explanation of the occurrence of subdural bleeding is difficult.

Although the number of patients with dementia praecox in mental hospitals is greater than that of patients with dementia paralytica, and although more of the former come to autopsy, the fact that 35 cases in each group showed subdural bleeding indicates a much greater frequency in patients with dementia praecox. This does not seem consistent with the fact that organic changes which favor subdural bleeding, such as vascular disease, brain atrophy and hydrocephalus, are frequently present in cases of general paresis. Both psychoses may be regarded as equally liable to physical trauma.

Epileptic patients with subdural hemorrhage (22 cases in 178 autopsies) form the next group in order of size. Among these the finding of subdural hemorrhage is readily explained by the frequency of seizures and the associated head trauma, resulting in skull fractures and in some cases brain damage.

Among the 22 epileptic patients, 11 died with fractured skulls. It was believed that the subdural hemorrhage was directly due to recent head injuries and skull fractures, although it is conceivable that the bleeding found at the autopsy was due to previous head injury. There were 2 other epileptic patients with recently fractured ribs, a total of 13 cases with known major trauma out of 22 epileptic patients in whom hemorrhage was found. The factor of trauma seems more important than the possibility of brain changes with advancing age. Exactly half the epileptic patients were under fifty years of age.

For purposes of classification, 4 cases of tabes dorsalis were included among the "psychoses with other brain and nervous disease," since there was some doubt whether syphilis was the sole etiologic factor in these patients.

There were 16 cases with alcoholic psychoses. The factor of alcoholism is only remotely related to the subdural hemorrhage, since most of the alcoholic patients were over fifty years of age and had been hospital residents for a long time. None were under thirty years of age. There were 2 between thirty and forty, 3 between forty and fifty, 5 between fifty and sixty and 6 between sixty and seventy. The mean age was fifty-four.

The use of alcohol was not the exclusive factor in producing psychoses among these patients. Personality defects were common, and unspecified neurologic disease may have been masked by the symptoms of alcoholism in many cases. Head injury following drunkenness is a remote possibility because of the long hospital residence. In a few of these cases there had been known trauma of various kinds. Trauma as a direct and exclusive factor was found to account for only 3 cases.* Organic brain disease and birth trauma may help to produce the condition.

Eleven cases of subdural hemorrhage were found in patients diagnosed as having psychosis with mental deficiency. They were distributed in the various age decades as follows: 2 each in the second, fourth and fifth, 4 in the sixth and 1 in the seventh.

In the affective disorders, subdural hemorrhage was a comparatively rare finding. There were 8 cases with manic-depressive psychoses and 5 with involutional melancholia.

The studies of subdural hemorrhage cited above are in general agreement as regards the importance of senility, syphilis, alcohol and trauma in producing the condition. In our study the cases cited may be rearranged to corroborate the earlier findings in part. There were 79 cases with psychoses associated with old age, that is, psychoses accompanying cerebral arteriosclerosis and those due to senile changes. Thirty-eight patients had been committed because of syphilis of the central nervous system (dementia paralytica and psychoses with cerebral syphilis). Sixteen cases with alcoholic psychoses and 3 with traumatic psychoses have been discussed. The factor of senility can be considerably emphasized if the elderly cases with dementia praecox and other psychoses are considered. In these, the patients had lived for years in a mental hospital before death.

Other psychiatric diagnoses were represented by a few cases. The seven minor diagnostic groups totaled only 18 cases.

The factor of nutrition and vitamin reserve is probably a significant one. It is at present receiving great attention, and will doubtless tend to modify the prevailing concept that trauma is the most serious etiologic factor in this condition, when the incidence of subdural hematoma in a group of patients with infrequent history of trauma is compared with the incidence in

*Obviously this figure is not representative, for the diagnosis was not made during life or even suspected by the clinical condition of these patients. The diagnosis of subdural hemorrhage in almost every case was made at postmortem examination. Head injury was the obvious factor in producing the 3 cases of traumatic psychoses, but trauma as an etiologic factor may have been overlooked in a large number of elderly, infirm patients, unsteady in gait, who had suffered falls and fractures, those with hyperactive behavior, irritable moods and combative dispositions and those with special accidents resulting in bruises, contusions, lacerations and fractures, with or without head injury. Thus, trauma appears more important in producing subdural bleeding among psychotic patients than it is in producing psychotic behavior.

a large series of cases with known severe head injuries. In the series of cases with severe head injuries reported by Munro the incidence was 18 per cent, while in our series it was 7.9 per cent.

It was possible to ascertain in 209 cases whether the lesion was unilateral or bilateral and, if unilateral, whether the lesion was on the right or left side (Table 3). Most hemorrhages were found

TABLE 3. *Location of Subdural Hemorrhage.*

LOCATION		NO. OF CASES
Unilateral or bilateral		
Unilateral		122
Right	64	
Left	58	
Bilateral		87
Unstated		36
On convex surface or base		
Solely convex surface		207
Solely base		20
Convex surface and base		18
Brain area*		
Frontal area		27
Parietal area		23
Temporal area		13
Occipital area		12
Cerebellar area		1

*Fifty cases are represented in this subgroup. In several, more than one area was involved.

over the convex surface of the brain and relatively few were exclusively over the base. In many cases, the subdural bleeding, although its presence was noted, was not fully described with respect to location. However, the descriptions were sufficiently accurate in 50 cases to state exactly which regions of the brain were mainly affected. In some cases more than one region of the brain was involved, — for example, the frontoparietal or the temporoparietal areas, — but the lesions in the frontal or parietal areas predominated. They were involved twice as frequently as the temporal and occipital regions. In at least half the cases the lesion was unilateral, as previously noted by Leary,[8] and this finding is important from an etiologic standpoint. Diseases of the blood vessels, the chief cause of brain atrophy (if accepted in any case as the sole cause of bleeding), is usually bilateral in distribution and should accordingly cause bilateral hemorrhage. The cases of subdural hemorrhage in patients with dementia paralytica were more frequently bilateral than was the case in other groups.

Extreme variations were noted in the size of the lesions. A few were described as small, circumscribed hemorrhages amounting to little more than "subdural flecking." In these, definite areas of bleeding could be seen under the dura, small in size and without evidence of the effects of pressure on the underlying brain tissue. They were probably fresh lesions in many cases, and possibly terminal in origin. This appearance was very pronounced in patients dying of respiratory disease, for example, pulmonary tuberculosis. A few lesions of this type were noted in epileptic patients who died of asphyxia.

The majority of hemorrhages were large and diffuse and usually involved considerable subdural space and extensive areas of the brain. It was common to find lesions extending over an entire lobe or pressing on the major part of the surface of two or more lobes, or even on the entire hemisphere. Lesions were frequently found which pressed on two hemispheres, or occasionally one hemisphere and the corresponding basal surface of the brain. The lesions varied in consistence from that of fresh blood to that of calcification, with the intermediate state predominating in which membranes surrounded the clotted blood, suggesting the formation of subdural cysts.

A rough determination of the age of the lesion was made from the condition of the blood. Liquid blood or a soft clot without a membrane was accepted as evidence of a recent lesion. Membrane formation with orange-brown pigmentation of the inner dural surface was taken as evidence that the hemorrhage was old. Every stage between these points was found, but the latter was commoner. It is noteworthy that atrophy was occasionally more marked beneath these rusty areas. Two extreme cases were found in which a layer of definite calcification had formed beneath the dura. Both occurred in mentally defective patients, and the lesions may have been the result of injury at birth. These cases showed positive evidence of recurrent subdural bleeding, and blood in all states, as well as membranes in several areas, was present. Multiple membranes were described occasionally in cases of dementia paralytica with subdural hemorrhage.

The age distribution demonstrates the increase in subdural hemorrhage with advancing years, but also shows that the condition is not unknown in earlier years. The psychiatric diagnosis in this series shows the relation of organic brain changes to subdural bleeding. Subdural hemorrhages in the insane appear to be a relatively unimportant cause of death. When venous congestion occurred before death, the subdural blood consisted of small, discrete and apparently recent hemorrhages, which were considered to be terminal phenomena. They were found mainly in epileptic patients, in those with dementia paralytica dying during convulsive seizures and in some with pulmonary tuberculosis and pneumonia.

There seems to be little connection between the age of the lesion and the duration of the psychosis except in a few acute cases with a fatal termina-

tion soon after admission. In a few cases, mental deficiency may have been caused by subdural hemorrhage together with birth trauma, but it is possible that there was other cortical damage.

In certain cases, rusty pigmentation and membrane formation on the inner side of the dura suggest that the lesions were at least one year or more in age. In some cases there was a blood clot of recent origin as well as one surrounded by a membrane, showing that a recurrence of bleeding is possible. This was best illustrated in cases of dementia paralytica and mental deficiency.

Summary and Conclusions

Two hundred and forty-five cases of subdural hematoma were found among 3100 consecutive autopsies of psychotic patients, an incidence of 7.9 per cent.

Presumable etiologic factors, such as trauma, avitaminosis, senility, alcoholism and syphilis, are discussed.

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CLINICAL AND POTENTIAL ALLERGY IN FAMILIES WITH ALLERGIC CHILDREN*

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THE incidence of clinical allergy in the general population has been variously estimated between 7 and 10 per cent. Such estimates have been based on surveys compiled by Cooke and Vander Veer,[1] Piness and Miller,[2] Vaughan,[3] Rowe[4] and others. Similarly, the incidence of clinical allergy in the families of hypersensitive patients has been placed between 40 and 60 per cent. These calculations have been based on case histories alone. Sometimes such histories are taken casually, with little attention paid to some of the less spectacular symptoms, which, nonetheless, often suggest allergy.

The incidence is of interest partly because the inheritance of allergy merits a more careful study, and partly because the early recognition of allergy in the family can frequently lead to a prevention of symptoms. It was decided, therefore, to apply the same method of investigation to the entire family as is applied to the individual allergic child. To this end, when a child with definite allergy applied for treatment, all other members of the immediate family available at that time were subjected to the same allergic survey as was the patient.

The survey consisted first of all in questioning about manifestations of past and present allergy, noting especially hay fever, vasomotor rhinitis, asthma, eczema, urticaria and angioneurotic edema. Skin tests were made on each patient and relative alike, as well as on a few normal control subjects. Estimates of blood eosinophils were not made.

There were 40 allergic patients; their relatives comprised 135 individuals. At the same time, four normal or control families with a total membership of 17 persons were investigated. All ages were included in the relatives and controls.

The relatives of the 40 patients comprised 32 fathers, 40 mothers, 30 brothers and 33 sisters. Of these, 40 (30 per cent) presented evidence of either present or past allergy as determined from their histories. None of the 17 members of control families, on the other hand, gave evidence in their histories of any of the common manifestations of allergy.

Skin tests were made by the scratch (dermal) method, and 35 different substances to which subjects are commonly sensitive were applied. In all, 6912 scratch tests were done, 6300 among allergic children and their families and 612 among the four control families. The same technic and the same substances were applied to the 40 patients,

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the 135 relatives and the 17 control subjects; a total of 192 persons. The results are presented in Table 1, in which the various antigens have been listed according to the frequency with which they caused positive skin reactions. The table does not include those antigens which were positive in less than 6 cases. Cocoa, vanilla, chicken feathers, cottonseed, kapok, beef, lobster and carrots caused reactions in 5, or 2.5 per cent, of the 192 subjects. Birch, rye, corn, barley and fish did so in only 4 (2.0 per cent) and beef in 3 (1.5 per cent), while milk and chicken gave positive results in only 1 case (0.5 per cent).

Table 1 shows that in the 40 children with frank allergy, 11 per cent of all the skin tests were positive. The relatives have been divided into two groups: those who gave a history of some manifestation of allergy in the past or present and so were considered allergic (*A*), and those who failed to give such a history and so were classed as normal (*N*). Thus, 10 of the 32 fathers were allergic by history, and 5 per cent of the 360 tests made on them were positive. On the other hand, the 22 non-allergic fathers showed an incidence of 2 per cent of positive tests. Likewise, the allergic mothers had three times as many positive tests as did the non-allergic mothers, 10 per cent and 3 per cent respectively, and the allergic brothers and sisters had a correspondingly higher ratio of skin tests than did their non-allergic mates.

In contrast to these results, the total incidence of positive skin reactions in the 17 members of the four control families was less than 1 per cent. These results are in fair agreement with those of Peshkin and Rost,[5] who found 0.76 per cent positive and doubtful reactions in 9406 skin tests on normal children.

These figures show clearly that the skin test is still an index of the patient's allergic disposition, and that the more active the allergy, the greater is the incidence of positive reactions. More striking, however, is the fact that the normal subjects among allergic families react more frequently than do those of control families, over 2 per cent against less than 1 per cent.

TABLE 1. *The Incidence of Positive Scratch Tests in 40 Allergic Children, in 135 Relatives and in 17 Non-Allergic Adult Controls.*

ALLERGEN	40 ALLERGIC PATIENTS	135 RELATIVES: FATHERS 10A	FATHERS 22N	MOTHERS 13A	MOTHERS 27N	BROTHERS 8A	BROTHERS 22N	SISTERS 9A	SISTERS 24N	17 NORMAL CONTROLS	TOTAL
House dust	21	3	4	4	6	3	3	2	2		48
Ragweed	17	4	1	3	3	3	4	4	2	2	43
Timothy	11		1	1			1	2	2		18
Cat dander	8		1	1	3		2			1	16
Orris root	5	1		1	5	1	1				14
Potato	9	1		2	1						13
Horse dander	5		1	1	3	1		1			12
Rabbit hair	2		1	3	3		3				12
Apple	5	2	1	1	1		2				12
Oats	7	1						1			9
Banana	5		1	1	1			1			9
Oak	3	1		2			1		1		8
Dog dander	2	1		3	1		1			1	9
Egg	5			1		1					7
Orange	4			3							7
Pear	4			2	1						7
Beans	2		3	2							7
Walnuts	4	1		1							6
Wheat	4	1	1								6
Tomato	3		1	2							6
16 other allergens	33	3	2	13	5		2	5	2		65
Total positive tests	159	19	18	47	33	9	20	16	9	4	334
Total tests made	1440	360	792	468	972	288	792	324	864	612	6912
Percentage of positive tests	11.0	5.3	2.3	10.0	3.4	3.1	2.5	4.9	1.0	0.7	4.8

The discrepancy between positive skin tests and symptoms is always important, and as a matter of incidental interest we attempted to correlate the clinical findings with the skin reactions in all patients tested. The data thus gathered are presented in Table 2. It shows, as expected, that wherever a history of frank allergy was present the skin tests were usually positive. The reverse is true where a history of allergy was lacking. The figures here also emphasize the relatively high in-

TABLE 2. *Correlation between the Allergic History and the Skin Tests in 175 Members of Forty Allergic Families.*

SUBJECTS TESTED	ALLERGIC HISTORY: SKIN TEST POSITIVE	ALLERGIC HISTORY: SKIN TEST NEGATIVE	NON-ALLERGIC HISTORY: SKIN TEST POSITIVE	NON-ALLERGIC HISTORY: SKIN TEST NEGATIVE
Allergic children (40)	31	9	0	0
Fathers (32)	7	3	6	16
Mothers (40)	8	5	10	17
Brothers (30)	5	3	8	14
Sisters (33)	5	4	6	18
Totals	56	24	30	65

cidence among the allergic families of individuals who have positive skin tests in the absence of clinical hypersensitivity. That such reactions may be of potential significance has been emphasized by Peshkin and Rost.[5]

Another observation made in the course of this study concerns the frequency with which more than one member of an allergic family may be affected. Thus, eleven families each had 1 member with allergy, twenty-one families had 2 members each, five had 3 each, and three had 4 each.

Discussion

Certain facts brought out in this study are of direct interest, others of inferential importance.

Of direct interest are the observations that potential allergy is common in each family that has one member with frank allergy. This is evident from the histories of the individual cases and from the number of positive skin tests among the normal members of such families. These potential allergic persons are a challenge to the clinician. If allergy is ever to be successfully treated, it must be recognized before the disease has progressed to an advanced stage. The elimination of wheat, milk or feathers in a patient with corresponding positive skin tests who has only minor symptoms, such as nasal stuffiness or a hacking cough, may ward off a much more serious illness, such as asthma or chronic sinusitis. Kern[6] has recently stressed this point. Particularly in children are preclinical allergic symptoms of allergy common. These early nasal and bronchial symptoms pass off as "colds," "bad tonsils" or "enlarged adenoids," only to assume a form of frank allergy at an older age.

The frequency with which more than one person in a single family may be allergic bears on the need of a comprehensive survey of all members of such families.

The patient's history is the best guide to the diagnosis of allergy. Exhaustive questioning of the members of our group, with particular attention to the occurrence of symptoms in relation to season, occupation, foods, drugs, environment and so forth, has enabled us to discover definite allergy in subjects who would otherwise have been classified as normal.

The skin tests, whose importance as a diagnostic aid has often been questioned, appear to be a definite and assertive index of allergy.

Summary

The incidence of clinical allergy is much higher in families with allergic children (46 per cent) than is that among the general population (7 to 10 per cent).

There is a greater incidence of potential allergy among members of allergic families than among members of normal families.

The frequency with which several individuals in single families are allergic bears on the need of comprehensive allergic surveys in these families.

The early recognition of subclinical allergy in allergic families and the elimination of possible sensitizing agents offer an approach to prophylaxis in allergy.

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REPORT ON MEDICAL PROGRESS

TRANSFUSION THERAPY*

A Review of Blood Groups, Transfusion Accidents, Hemolytic Reactions, Stored Blood, Transfusion Methods, and Plasma and Serum Transfusions

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THE major advances in transfusion therapy in recent years have concerned the immunological aspects of blood groups, clarification of the mechanism of certain transfusion accidents, the increased use of stored blood (preserved blood, bank blood), the introduction of methods for preservation by drying of plasma and serums‡, and the use of dilute and concentrated plasma or serum for transfusion. World War I gave great impetus to the transfusion of whole blood containing citrate as an anticoagulant and introduced the use of stored blood on a moderate scale. In World War II it is apparent that stored whole blood, plasma and serum will be tried on a large scale. During the last year two valuable books on blood groups and blood transfusion have been published: the second edition of Wiener's[1] book is an important source for information on transfusion, the technic of blood typing and especially the immunology, heredity and anthropology of blood groups; Riddell's[2] new volume is a most practical treatise on transfusion therapy based on his wide experience. These two books complement each other remarkably well.

The frequency of blood transfusions is a matter of common knowledge.[3] The indications for transfusion of whole blood and of plasma or serum are undergoing change, and depend on what elements of the blood are specifically required by the patient. The major uses for the transfusion of whole blood have been, and still remain, the replacement of hemoglobin for its oxygen-carrying power, and the combating of shock due to loss of blood volume. In bleeding disorders, such as hemophilia, thrombocytopenic purpura and the hypoprothrombinemia of vitamin K deficiency, transfusions of whole blood may be lifesaving. Many transfusions are given for supportive treatment, and some for the immune properties of the plasma.[4] It remains to be seen how widely plasma or serum will be employed for the treatment of shock and for the replacement of proteins, prothrombin, clot-promoting substances in hemophilia,[5] immune bodies and readily available foodstuffs. It is noteworthy that dogs on a protein-free diet can be maintained in nitrogen equilibrium by the parenteral administration of dog plasma.[6] Bock[7] and Riddell[8] have discussed the possible contraindications to transfusion in such conditions as cardiac failure, nephritis, protein sensitivity, hemolytic anemia, leukemia and lymphoma.

The major source of blood for transfusion therapy in the United States is the professional donor.[3] The cost[3, 9] of 500 cc. of blood varies from $25 to $50. For indigent patients this cost to the family or institution may become economically prohibitive. One large municipal hospital paid $14,825 in 1939 to professional donors for urgent transfusions. In contrast with the professional system, the British Red Cross Society in 1921 established the voluntary system, in which the donor receives no payment except for traveling expenses, usually amounting to an equivalent of 25 cents. The London service alone had 2378 volunteer donors registered and supplied 6628 transfusions in 1937. Riddell[10] devotes two chapters to a thorough description of the merits and organization of this remarkable service. He emphasizes the low cost — about $2.25 per transfusion — for administration costs, the high type of donor obtained, the freedom of donors from syphilis, and the method of supervision of the donor's health, which limits the number of times blood may be given to four a year for men and three for women. This volunteer system has proved practical and economical to administer, and permits the unlimited use of transfusions for indigent patients without undue burden to patient or hospital. The administrative costs are defrayed by income derived mainly from fees from private cases, with a smaller contribution by public institutions.

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‡Plasma is the fluid portion of unclotted blood, usually separated from the cellular elements after the addition of an anticoagulant. Serum is the fluid portion which is separated from clotted blood.

Blood Groups

It is of interest to review the recent advances in the immunological aspects of blood groups because of the practical application of these facts in transfusion therapy.

Classifications of Blood Groups

The extensive use of both the Jansky and the Moss classifications of blood groups has caused confusion[3, 11] because of their conflicting numbers for Groups O and AB of the international nomenclature. As shown in Table 1, the international nomenclature classifies the blood groups according to the presence or absence from human red blood cells of the two agglutinogens,* A and B, which are the dominant hereditary factors discovered by Landsteiner.[11, 12] The international nomenclature was accepted by the Public Health Committee of the League of Nations in 1929 and is used extensively in scientific publications. It has definite advantages, compared to the numbering systems, since it is free from ambiguity and is based directly on the physiology and genetics of the blood groups. Undoubtedly the international nomenclature should be taught in medical schools and introduced into hospital usage to replace the less definitive classifications of Moss and Jansky.

Table 1. *Classifications of Blood Groups and Subgroups of Human Blood, Showing the Agglutinogens of the Red Blood Cells and the Isoagglutinins of the Plasma and Serum.*

Classifications of Blood Groups				Agglutinating Sensitivity of Red Blood Cells	Isoagglutinins Usually Present in Plasma and Serum	Isoagglutinins Occasionally Present in Plasma and Serum	Frequency of Groups and Subgroups in 904 Individuals in United States[21]
Moss Numbering	Jansky Numbering	International Nomenclature* Group	Subgroup				
IV	I	O			a, a_1, β		44.5
II	II	A	A_1	Strong	β	a_2 (rare)	25.6
			A_2	Moderate	β	a_1	12.0
III	III	B		Strong	a, a_1		13.6
I	IV	AB	A_1B	Strong or moderate		a_2 (rare)	3.1
			A_2B	Weak		a_1	1.2

*Groups and subgroups named for agglutinogen of red blood cell; group O red blood cells do not contain A or B agglutinogen; one with Group O blood is the so-called "universal donor," and one with Group AB the "universal recipient."

a isoagglutinin agglutinates all red blood cells containing A agglutinogen (Subgroups A_1, A_2, A_1B and A_2B).

a_1 isoagglutinin agglutinates only red blood cells containing A_1 agglutinogen (Subgroups A_1 and A_1B).

β isoagglutinin agglutinates all red blood cells containing B agglutinogen (Group B and Subgroups A_1B and A_2B).

a_2 isoagglutinin agglutinates red blood cells containing A_2 agglutinogen (Subgroups A_2 and A_2B [weak]) and also those of Group O blood.

Determination of Blood Groups

Samples of human blood are subdivided into four different groups by observing the presence or absence of agglutination in a mixture of human red cells and serum. When agglutination results, it is the specific reaction between the agglutinogen of the red blood cell and the corresponding isoagglutinin† of the serum. Thus, A agglutinogen is agglutinated by a isoagglutinin but not by β isoagglutinin; and similarly, B agglutinogen is agglutinated by β isoagglutinin but not by a isoagglutinin. As shown in Table 1, corresponding agglutinogens and isoagglutinins do not exist in the same blood; on the contrary, those isoagglutinins are present in the serum for which there is no corresponding agglutinogen in the red cells. Accordingly, the blood group of an unknown blood sample may be determined in two ways:[12] by identifying the agglutinogen content of the red cells, employing test serums of known blood groups; by identifying the isoagglutinin content of the serum, employing test red cells of known blood groups. Since test serums may be conveniently stored they are used routinely for the determination of blood groups, but the use of test red cells is a valuable adjunct to the use of serums.

In the usual technic, three reagents are necessary — a suspension of the red cells to be examined and the two test serums, which are derived respectively from blood of Groups A and B. The blood group is determined by observing the presence or absence of agglutination between the unknown cells and the two test serums. The serum from Group A contains β isoagglutinin, that from Group B contains a isoagglutinin. Accordingly, red cells of Group O are not agglutinated by either serum since these cells contain neither

*The specific agglutinable property of the erythrocyte.

†This term refers to the origin of the agglutinin in the human species, as opposed to a heteroagglutinin from another animal species.

A or B agglutinogen. The cells of Group AB, however, are agglutinated by both test serums since both agglutinogens are present. The cells of Group B are agglutinated by only one test serum, that is, Group A serum containing β isoagglutinin; cells of Group A, on the contrary, are agglutinated only by the test serum from Group B containing the a isoagglutinin. A variety of technics have been found satisfactory, such as the hanging drop[11] and slide methods,[12] the test-tube procedure of Landsteiner,[11] and the macroscopic technic of Riddell[13] employing undiluted whole blood. The most important safeguard in blood grouping is the use of test serums containing high concentrations of isoagglutinins.[12, 14–16] Riddell[16] advises using only those test serums which produce agglutination at a dilution of 1:100. Satisfactory test serums may be purchased from the Transfusion Betterment Association of New York City and from certain pharmaceutical companies. The concentration of isoagglutinins in any serum can be determined readily by testing serial dilutions of the serum with known red cells, as described by Wiener[12, 17] and by Riddell.[18]

It has been shown that blood of Groups A and AB can be subdivided, by qualitative differences in A agglutinogen, into Subgroups A_1, A_2, A_1B and A_2B.[19] For a review of this subject Wiener[20] should be consulted. The approximate frequency of occurrence of the subgroups in the United States, as reported by Wiener and Rothberg,[21] is shown in Table 1. There are important practical aspects of the subgroups which concern the routine grouping of blood. The relative average sensitivity, in the agglutination reaction, of the agglutinogens of the subgroups can be represented as follows: $A_1 > A_1B > A_2 > A_2B$.[22] Furthermore, the a isoagglutinin agglutinates all cells containing A agglutinogen, whereas the a_1 isoagglutinin agglutinates only the A_1 agglutinogen. The concentration of a and a_1 isoagglutinins varies widely in serums from bloods of Groups O and B. Such serums containing low concentrations of these isoagglutinins when combined with the weakly sensitive cells of Subgroup A_2 or A_2B, may fail to produce agglutination in both the indirect grouping test and in the direct crossmatching.[20, 23] Under these circumstances, Subgroup A_2 blood can be incorrectly grouped and crossmatched as Group O (no agglutination observed) and Subgroup A_2B incorrectly designated as Group B (agglutination only by β isoagglutinin).[15] Weak test serum is the direct cause, therefore, of such errors in grouping and is probably responsible for a significant portion of those Group A bloods which are incorrectly grouped as Group O. For a description of methods for identifying the subgroups, see Wiener[20] and Davidsohn.[23]

Isohemolysins

Isohemolysins are a normal component of human serum and are demonstrable in about 30 per cent of serums containing isoagglutinins.[11] These isohemolysins are group specific, producing hemolysis of the same cells which are agglutinated. Although the isohemolysin cannot be separated from the isoagglutinin, the hemolytic reaction requires the presence of serum complement, whereas the agglutination reaction does not. Since isohemolysins frequently are not demonstrable, it is possible to have isoagglutination without isohemolysis, but isohemolysis is always associated with isoagglutination. The largest dilution of a serum that still shows isohemolysis is usually much lower than that dilution still showing isoagglutination. Practically, isohemolysis may occur and may interfere with the agglutination in the direct compatibility test when fresh serums containing complement are used.[11]

Problems in Blood Grouping

From the practical point of view, if the two test serums contain a high concentration respectively of a and β isoagglutinins, there is rarely any difficulty in classifying red cells correctly into one of the four blood groups (O, A, B and AB). The most dangerous error in blood grouping results from a failure to obtain agglutination, resulting usually from weak test serums.[14, 23] A striking case, reported by DeGowin,[24] is that of a donor, incorrectly grouped, who served as a Group O donor in ten transfusions. After three years, when potent testing serum was used, he was found to belong to Group A. The discovery was not made, however, until two patients of Group O had died from hemolytic reactions. Since the crossmatching of donor's and recipient's bloods appeared compatible in these fatal accidents, this emphasizes the limitations of the compatibility test and the danger of incompatible blood mixtures which do not show agglutination in vitro at room temperature.

In the direct compatibility or crossmatching test, which should be performed before each transfusion, apparent incompatibilities are occasionally observed, as evidenced by agglutination.[14, 25] In certain cases, agglutination is expected from a knowledge of the blood groups. For example the serum from Group O should agglutinate the red cells of the other three blood groups. In other cases, agglutination may occur that is not expected from the blood groups involved. In this event it is advisable to carry out the following proce-

dures: recheck the blood grouping; examine the agglutinating potency of the testing serums with known cells; and determine whether the unknown serum agglutinates the red cells from that same individual (autoagglutination). Rouleau formation or pseudoagglutination if observed with undiluted serum is usually eliminated by diluting the serum with an equal volume of physiological saline. So-called "autoagglutinins" may produce agglutination at room temperature of all red cells, including those of the same individual. This reaction is increased at ice-box temperatures and is completely reversible at body temperatures. The presence of rouleau formation of autoagglutinins in the recipient's serum is not a contraindication to transfusion. Incompatibilities have been observed[20, 23] between the subgroups of Groups A and AB due to the agglutination of the red cells of one subgroup by the isoagglutinins occasionally present in the serum of the other subgroup, as shown in Table 1. A chapter of Wiener's[14] book is entitled "Sources of Error in Blood Grouping."

*Blood Types**

Landsteiner and Levine have described other agglutinogens of human red cells, designated as M, N and P, which are demonstrated by agglutination reactions with immune rabbit serums. These agglutinogens appear to have no immediate clinical importance in transfusion therapy per se[26] but have a well-established significance in the hereditary and medicolegal aspects of blood groups.[27] For a review of these blood types, see Wiener.[28] As stated by Wiener and Peters,[26] "With the agglutinogens A_1, A_2, B, M, N, P and Rh, alone, as many as seventy-two different types of human blood are readily distinguished." This fact is staggering, but for the clinical use of transfusion therapy it is essential to consider primarily the blood groups of the international nomenclature, and possibly in addition Type Rh, which is discussed below.

Transfusion Accidents

The mortality rate from transfusion accidents estimated from large series varies from 0 to 0.5 per cent.[3, 24, 29] Many such deaths are preventable. The reported frequency of nonfatal reactions, including febrile responses, to transfusion is significantly higher, varying from 1 to 40 per cent.[3, 30, 31]

Fatal transfusion accidents involving the recipient may be roughly classified as follows:[32, 33] hemolytic reaction, with death from shock or later from uremia; congestive heart failure or vascular accidents, such as embolism and intracranial hemorrhage; allergic response, with bronchial spasm[3, 33]; hyperpyrexia,[3] occasionally reaching temperatures of 112 and 115°F.; operative accidents, such as air embolism or intracranial hematoma following transfusion through the fontanel.[3] Nonfatal reactions include the above accidents in milder form, the transfer of diseases such as syphilis, malaria and influenza,[3, 33] and the operative complication of phlebitis. The blood donor occasionally suffers the complication of anemia, syncope or phlebitis, but only with great rarity has death been reported.[3] The prevention of accidents is certainly a most important aspect of transfusion therapy.

Fatal and nonfatal transfusion accidents are in large part preventable, provided their causes are understood and avoided. The problems of hemolytic reactions and the compatibility of bloods are discussed subsequently in some detail. The incidence of chills and fever following transfusion can be reduced from 12 to 1 per cent[30] by the elimination of foreign proteins, including clotted blood, from the transfusion equipment and of "pyrogenic" organisms[34] from the distilled water that may be used. The proper preparation of solutions, instruments and equipment has been well described by Lewisohn and Rosenthal.[30] Congestive heart failure is usually a contraindication for blood transfusion. In patients without manifest heart disease, however, fatal shock or congestive failure has occurred following severe rigor or an apparently uncomplicated transfusion. Altschule and Gilligan[35] have recently shown that in normal subjects the infusion of solutions of salt or dextrose at the rate of 20 cc. per minute produces an increase in blood volume but only minimal changes in the cardiovascular functions. At more rapid rates they observed an increase in blood volume, together with considerable increases in venous pressure and cardiac output and changes in the electrocardiogram. Many serious reactions would be prevented by the slow administration of blood with an intravenous drip technic and at a drip rate of 40 to 60 drops per minute.[2] The danger of allergic response in asthmatic or hypersensitive patients may be decreased by the biological test described below, and by insisting that the donor be in a fasting state before giving blood. The transfer of syphilis, malaria, influenza and other diseases is controllable by proper selection of the donor. Also, it is frequently possible to anticipate that a patient may require a transfusion. The completion of the arrangements in advance will remove much of the emergency status, which is

*The bloods containing agglutinogens identified by heterologous (animal) serums are assigned to certain types (M, N, P and Rh)[27] in order to distinguish them from the blood groups (O, A, B and AB), which are identified by homologous (human) isoagglutinins.

conducive to making errors. Operative accidents can be reduced to a minimum by employing well-designed simple equipment[31] and by avoiding cutting down on veins, a procedure which is rarely necessary.

Hemolytic Reactions

The rapid intravascular hemolysis in the recipient of the donor's or recipient's red blood cells, with liberation of massive amounts of free hemoglobin, constitutes the most frequently dangerous complication of transfused blood. The pathogenesis of shock following a hemolytic reaction and treatment by an immediate second transfusion of compatible blood are described by Hesse and his co-workers.[36] The reports of Bordley[37] and of DeGowin and his collaborators[38, 39] on the kidney lesion produced by hemoglobinuria deserve detailed study.

Mechanism of Increased Blood Destruction

There is general agreement that increased blood destruction may result from the admixture of red blood cells with plasma containing incompatible agglutinins, hemolysins or both.

It has been clearly demonstrated that hemolysins occurring without agglutinins may produce extreme intravascular hemolysis.[40, 41] Conversely, Ham and Castle[42, 43] have recently shown that the injection into animals of an agent producing extreme agglutination of erythrocytes, but without hemolytic activity in vitro, causes hemolytic anemia, hemoglobinemia, spheroidal erythrocytes and increased susceptibility of the red blood cells to hemolysis in hypotonic solutions of sodium chloride (fragility test). They also demonstrated that sterile incubation of mammalian blood in vitro and intravascular stasis in vivo produce similar changes in the erythrocytes. Consequently, they believe that hemolytic transfusion reactions caused by agglutinins (without hemolysins) may result from the intravascular stasis of agglutinated red cells in the spleen and other organs. As in the test tube, hemolysis results from progressive swelling of the red blood cells to the point of rupture, apparently due to an increase in the osmotically active constituents of the erythrocytes.[42, 43] Similar observations on the effect of stasis on the fragility of erythrocytes have been recently reported by Tsai, Lee and Wu.[44]

In this connection, Wiener and Schaefer[45] have shown that the erythrocytes of blood stored for twenty-one days were destroyed by the recipient in twenty-four hours, with resulting hemoglobinemia and hemoglobinuria. Red cells stored for so long a period are known to show swelling and a marked increase in hypotonic fragility.[46–48] Presumably they are destroyed in vivo by the above mechanism of further swelling and rupture, which is quite comparable to the destruction of red cells of increased fragility in hemolytic jaundice.[42, 43]

Blood Compatibility

Most hemolytic reactions result from the transfusion of incompatible blood; some result from stored blood that is too old.[31, 45] Fatal hemolytic reactions have resulted when blood of known incompatibility was given, but also when no incompatibility could be demonstrated in vitro. There are, therefore, at least two major problems: the avoidance of incompatible blood transfusions, and greater care in detecting incompatibilities.

The only bloods that are potentially compatible are those belonging to the same blood group and, probably, to the same subgroup.[23, 26] Even here homologous group incompatibilities are demonstrable, as shown below.

The use of Group O blood, from the so-called "universal donor," to transfuse individuals of the other three blood groups introduces plasma from the donor containing both α and β isoagglutinins, which are not compatible with the red cells of the recipient. Usually, however, these agglutinins are of relatively low concentration and are adsorbed by the red cells and diluted by the plasma of the recipient without harmful reaction. Although large numbers of such transfusions without fatalities are reported, there is a difference of opinion concerning the safety of this practice, as discussed by Riddell.[49] It is apparent that a number of fatal and nonfatal hemolytic reactions have resulted from the use of Group O blood containing large concentrations of α or β isoagglutinins or both.[3, 24, 29, 50, 51] Coca[52] found that these potentially dangerous universal donors comprised 3 per cent of 350 prospective Group O donors. Therefore, if universal donors must be available for emergency transfusions in other blood groups, it is probably essential to avoid those with a high concentration of isoagglutinins. The concentration of isoagglutinins can be determined readily by serial dilution of the serum, as described by Wiener[17] and by Riddell.[18]

Homologous Group Incompatibility. Fatal hemolytic reactions have occurred with disturbing frequency following the transfusion of blood apparently of the same group as the recipient's, or following multiple homologous group transfusions from the same donor.[24, 26, 53, 54] In many such cases competent observers have failed to detect in vitro any evidence of incompatibility. One promising advance toward understanding this type

of reaction is the recent description by Wiener and Peters[26] of Rh agglutinogen and Rh isoagglutinin in human blood. The Rh agglutinogen is independent of the A, B, M, N and P agglutinogens, and is detected by agglutination with serum prepared by immunizing rabbits with the red blood cells of a monkey *(Macaca rhesus)*.[55] Human bloods containing red blood cells agglutinated by the heteroagglutinin of this immune serum, and therefore showing the presence of Rh agglutinogen, are designated as Type Rh+. Of approximately 100 blood samples tested, those found to be Type Rh+ constituted about 85 per cent, and those found to be Type Rh– only 15 per cent. Accordingly, it is possible to have bloods of any one of the international blood groups which are either Type Rh+ or Rh–. Most donors' bloods are Type Rh+ and transfusion of this blood into an Rh– recipient of the same international blood group with a Type Rh– blood has produced an immune response, that is, the appearance of the Rh isoagglutinin in the blood of the recipient. Subsequent transfusion of Type Rh+ blood into the same recipient has produced reactions, presumably because of the destruction of the Rh+ red cells by the newly formed Rh isoagglutinin. Weiner and Peters emphasize that the agglutination reaction in vitro between Rh agglutinogen and Rh isoagglutinin is not strong and may occur only at cold temperatures. Two severe hemolytic reactions, one of them fatal, have been observed, however, following such homologous group transfusions, coincident with the appearance of Rh isoagglutinin in the serum of recipients with Type Rh– blood who received more than one transfusion of Type Rh+ blood. Wiener and Peters suggest the following technic in addition to the usual grouping and crossmatching procedures as a presumptive test for the presence of incompatibilities due to Rh factors.

Two drops of patient's serum, preferably separated from the clot at refrigerator temperature, are mixed with one drop of the donor's cell suspension in a small test tube (Tube 1).

In another tube a similar mixture of the patient's serum and the patient's cells is set up (Tube 2).

The tubes are placed in ice water for five minutes, then centrifuged while still cold, and the mixtures gently shaken. The agglutination reaction is observed macroscopically and microscopically. If neither tube shows agglutination the donor is compatible. If both show agglutination an autoagglutinin is present and the donor probably can be used without danger. If Tube 1 shows agglutination and Tube 2 does not, the donor is incompatible.

This evidence serves to re-emphasize the importance of crossmatching blood samples before any and every transfusion. It is possible that the above compatibility test may detect certain dangerous homologous group incompatibilities.

The subgroups of Groups A and AB have not yet been shown to produce hemolytic reactions[26] when transfusions have occurred within the group, that is, Group A_1 blood given to a Group A_2 recipient. If such reaction occurred, as pointed out by Wiener and Peters, it would be necessary also to rule out other sources of incompatibility, such as the Rh factor. However, it is advisable to avoid the transfusion of bloods that can be shown to be incompatible in the crossmatching. Thus far, Types M and N have not been shown to be related to hemolytic reactions.[26]

The Biological Test

The biological test has been emphasized as a valuable adjunct to the prevention of dangerous hemolytic reactions.[26] This test consists of the slow injection, that is, by intravenous drip, of 10 cc. or more of blood, with the observance of any symptoms occurring after twenty minutes of injection, such as chill, pain or restlessness. If the transfusion is stopped because of a severe reaction, it is unlikely that the injection of as much as 100 cc. of incompatible blood could produce a fatal hemolytic reaction.[26] Furthermore, the urine may be alkalinized in advance of transfusion by administering sodium bicarbonate by mouth[38, 39]; this simple prophylactic procedure may well prevent the kidney complications of hemoglobinuria.

Methods of Transfusion

Concerning the debated question of the direct as compared with the indirect methods of transfusion, Riddell's[56] statement is probably an adequate summary. "There is," he says, "no reasonable or convincing evidence that therapeutic priority can be awarded to or claimed by either whole or citrated blood, and it is the clinical experience of those who have used and studied both varieties that no difference exists in the results obtained." Both Riddell[2] and Wiener[1] give full descriptions of direct and indirect methods of transfusion.

Stored Blood

The use of stored blood for transfusion, begun in World War I,[57] has increased materially. Thus, Wiener[58] collected reports in 1939 of at least 14,000 transfusions of stored blood given in the United States. The technic of setting up a blood bank and collecting and storing blood has been fully described elsewhere.[31, 59–64] Exclusive of war work, the blood bank has been especially useful in large

charity hospitals, where blood from volunteer donors may be collected and used within a few days, and where expert supervision is available. Unquestionably, the proper use of stored blood is an important adjunct to transfusion therapy and, because of the presence of volunteer donors, offers economic assistance to the hard-pressed charity hospital.

The limitations[31, 45] of using stored blood vary in proportion to its state of preservation.* It has been demonstrated that the following changes occur, varying considerably with the type of medium mixed with the blood: the erythrocytes gradually swell, increase in fragility and eventually hemolyze[46–48]; the platelets and white blood cells decrease within twenty-four hours[47, 65]; the bactericidal and phagocytic activities are slowly reduced[65]; the prothrombin concentration gradually diminishes[66–68]; certain chemical changes are progressive.[69–73] The maximum period of storage of blood is debated in the literature and variously stated as from two days to two weeks, with most observers suggesting that the blood be used within a week. Red blood cells which are increased in fragility probably are destroyed, after transfusion, at a rate roughly proportional to their fragility. The reactions to transfusions of stored blood have been studied[31, 45, 74] but require more investigation.

Plasma and Serum Transfusions

Preliminary studies on animals and man are available concerning the transfusion of serum and of plasma, containing sodium citrate as anticoagulant, in the treatment of shock,[75–78] hemorrhage,[76] burns,[79] increased intracranial pressure[80] and hypoproteinemia,[81] and in the prophylactic treatment of infectious diseases.[82, 83] In most observations the plasma or serum was preserved by drying, employing one of several methods now available.[84–87] Such dried material is apparently preserved indefinitely; it may be redissolved readily and given in concentrated or diluted form. The use of preserved plasma will probably become an important part of transfusion therapy because of the availability of plasma from stored whole blood, the excellence of preservation, the ease of transportation and the convenience of administration. Theoretically, the indiscriminate transfusion of plasma or serum in large amounts without consideration for blood groups may produce dangerous reactions. The isoagglutinin concentrations may be reduced materially by pooling serums[88] or by mixing citrated blood samples, for example Groups A and B, such that the isoagglutinins and isohemolysins are absorbed by the red cells and thereby removed.[87] Plasmas or serums known to have low concentrations of isoagglutinins and isohemolysins could be administered, in all probability, without regard to blood groups.

*Use of the term "preserved blood" is less desirable than that of the term "stored blood," since progressive changes occur on standing.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTEMORTEM AND POSTMORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 26351

PRESENTATION OF CASE

A thirty-seven-year-old caretaker was admitted to the hospital complaining of headache of about five days' duration.

The patient was aphasic on arrival at the hospital, and the history was obtained from his wife. He had always enjoyed good health until the winter before admission, when he suffered with frequent, severe head colds, often associated with swelling over the left eye, and accompanied by the drainage of a profuse, thick, yellow nasal discharge. About six weeks before entry an abscessed tooth was extracted by his dentist. He was well thereafter until fourteen days before admission, when he developed another typical head cold. This persisted, but he continued to work, and four days before admission, while attending the cinema, the left eye began to "water." He developed a progressively increasing pain in it, and in the left supraorbital region, which radiated upward over the forehead. Three days before entry the pain was so severe that he remained home from work. There was no known fever. A local physician was called, who prescribed nose drops for sinusitis. He was recalled a few hours later to administer morphine for the pain which had become excruciating. Two days before admission the patient developed a fever of 102°F., and in the evening had a mild chill, with nausea and vertigo. The pain was located mostly in the midline of the forehead and vertex. On the morning before entry the patient, obviously worse, had a severe shaking chill, and shortly thereafter he developed aphasia and impairment in vision.

The past, family and marital histories were noncontributory.

Physical examination revealed a well-developed and well-nourished, acutely ill, weak, aphasic man. There were slight ptosis and edema of the left upper eyelid, with acute tenderness over the left frontal sinus. The neck was stiff to passive flexion. Because of poor co-operation, a funduscopic examination was impossible. The nose showed acute edema with no pus. The tongue was dry and coated, and there was thick tenacious mucus over the pharynx. Examination of the heart and lungs was negative. The blood pressure was 120 systolic, 70 diastolic. The bladder was palpated almost at the level of the umbilicus. The neurological examination showed that the patient's eyes moved normally toward the left, but failed to move or follow objects beyond the midline to the right. The pupils were round and equal and reacted to light. Corneal reflexes were present. The remaining cranial-nerve examination was unsatisfactory. The muscles of the right arm and leg were paralyzed; indeed one neurologist diagnosed a right hemiplegia with a right homonymous hemianopsia. The tendon reflexes in the arms were less active on the right side. Knee and ankle jerks were not obtained, and there was no plantar response on either side. There was no reaction to pinprick over the right leg, arm and face, but the left arm and leg were withdrawn when thus stimulated.

The temperature was 104.8°F., the pulse 88 and the respirations 24.

Examination of the blood revealed a red-cell count of 4,200,000 with 82 per cent hemoglobin, and a white-cell count of 29,000 with 80 per cent polymorphonuclears. The urine was negative. The blood Hinton and spinal-fluid Wassermann tests were negative. The blood nonprotein nitrogen was 37 mg. per 100 cc. A lumbar puncture showed a clear "yellowish" fluid with normal dynamics, a cell count of 427 per cubic millimeter with 400 polymorphonuclears, a ++ alcohol protein test, a total protein of 186 mg. per 100 cc., a sugar of 81 mg. and an essentially normal gold-sol curve. Two days later another lumbar tap revealed similar findings, except that the total protein was 258 mg. per 100 cc., and the sugar 100 mg.

Roentgenograms of the sinuses showed haziness in the left frontal ethmoid and the left antrum. There was normal aeration of the sinuses on the right, and no definite change in the bones adjacent to the sinuses. Skull plates showed no evidence of increased intracranial pressure.

The patient rapidly became more acutely ill. He developed twitchings of the right side of the face that were occasionally the precursors of generalized convulsions. He was given sodium luminal intravenously, and sulfapyridine intravenously to a blood level of 14.5 mg. per 100 cc. There was severe retching and vomiting. Small subconjunctival hemorrhages appeared in the right eye. The temperature, pulse and respirations rose on the second hospital day to 106°F., 140 and 50 respectively. Convulsions became more frequent, beginning with localized twitching of the right side of the face, and becoming generalized. There was a conjugate deviation of the eyes toward the left,

changing to the right during the convulsions. There was no apparent response to treatment. Stupor increased rapidly. The pulse became weak and rapid, cyanosis appeared, and death occurred on the third hospital day.

Differential Diagnosis

Dr. Harold G. Tobey: It is evident that we are dealing with an acute frontal sinusitis which was probably engrafted on a chronic process. We have a history of previous attacks of frontal sinusitis, as evidenced by headaches and occasionally some swelling of the left eye. Let us stop for a moment to consider the possible complications of an acute frontal sinusitis. Infection can extend in two ways. The first is by spread via thrombosed vessels through the posterior wall of the frontal sinus to the dura, and through the dura to the subdural space. The other way is by direct extension through the posterior wall, with necrosis of the bone. There is one significant entry here, that is, the extraction of the abscessed tooth. It is true that in the presence of sinus infection, both of the antrum and of the frontal sinus, the extraction of abscessed teeth may light up a previous infection which has been giving very few symptoms. There have been a number of these cases at the Eye and Ear Infirmary, the mode of extension probably being through the blood stream. We have had a number of cases in which, following extraction of teeth, there has been spreading osteomyelitis. However, this patient seemed to be well following the extraction up to fourteen days before admission, when he began to have further symptoms of infection of the frontal sinus, which became progressively worse. Then two days before entry he had a mild chill associated with nausea and vertigo. Knowing he had an acute frontal sinus the chill might possibly have been the beginning of a brain abscess. An acute brain abscess often is associated with chilly symptoms, nausea and vertigo. On the other hand, this may have meant a beginning blood-stream infection. The chill was accompanied by pain in the midline of the forehead and vertex. The situation of the pain is in the region of the frontal sinus, but with pain located in this area and with the chill, nausea and vertigo we also have to suspect the beginning of a phlebitis and thrombosis of the longitudinal sinus. The morning before entry there was another severe chill, and shortly thereafter the patient developed aphasia and impairment of vision. With the mention of aphasia, of course, we immediately begin to think of the rolandic area and the possibility of some septic focus there. It might possibly have represented the start of a brain abscess, of a localized meningitis over this area or possibly of an extradural abscess.

There were slight ptosis and edema of the left upper eyelid, with acute tenderness of the frontal sinus. This makes us think of perforation, either through the floor of the frontal sinus or from the ethmoid, and a beginning orbital abscess, but it was accompanied by a stiff neck, which of course immediately brings up the question of meningitis. We will come to that later in considering the spinal fluid.

Next we have the neurological examination and the matter of the eyes. He moved them to the left normally, but they did not go beyond the midline to the right. That perhaps is not an unusual finding. I know of no lesion except a central one that would cause that, and I think it is perhaps unimportant. The one important thing about the eyes was the absence of nystagmus. In these acute infections we have to think of metastatic abscesses and the possibility of cerebellar abscess, but the absence of nystagmus at this stage argues against a cerebellar lesion.

The next point of importance is the paralysis of the right arm and leg, which of course brings us back again to the left rolandic area. The superficial reflexes were present, but the knee jerks, Babinski and ankle clonus were absent, all of which argue for absence of any generalized meningeal infection. On the other hand we have the history of the stiff neck, which is one of the earliest signs of general meningeal infection.

The next important points are the results of the lumbar puncture. The fluid was yellowish, with normal dynamics, a cell count of 427 per cubic millimeter with 400 polymorphonuclears, and a questionable increase in the total protein and the sugar levels. Two days later another lumbar puncture was done, and again the fluid showed an increased protein and an increased sugar. These findings argue against any general meningeal infection. The initial pressure is not mentioned; I imagine it was increased. The 427 cells with the 400 polymorphonuclears are consistent with a local meningitis. The increased protein of course argues for cerebritis with destruction of some brain tissue, but again the practically normal or slightly elevated sugar is against any bacterial invasion of the entire meningeal fluid.

Dr. Charles Kubik: The initial pressure was 310 mm. of water.

Dr. Tobey: We know that with bacterial infection of the cerebrospinal fluid the sugar is practically always decreased, and this is also consistent with a localized and perhaps somewhat walled-off meningeal infection. We have no report of the

bacteriology of the spinal fluid, but I should imagine that no bacteria were found. X-ray films showed no evidence of osteomyelitis of the frontal bone, so that perhaps we can at this point rule out osteomyelitis. The absence of osteomyelitis means that there was probably no necrosis of the posterior wall — but that is not definite.

Things went from bad to worse, and the process, whatever it was, extended over the rolandic area. A right hemiplegia became obvious, including involvement of the right facial nerve, and he had convulsions which began on the right side of the face and became generalized.

The first possibility is extradural abscess from frontal sinusitis. The symptoms were altogether too marked and too serious for a simple extradural abscess. The next is brain abscess, but although the initial chill argues for a beginning acute abscess, the subsequent symptoms came on too rapidly. Abscess usually causes neurological symptoms, particularly hemiplegia, later in the disease. The aphasia, of course, could be caused by an acute abscess either in the frontal lobe or in the temporal lobe. With abscess in the frontal lobe aphasia usually develops rather late, not until the abscess extends and finally causes edema and pressure over the temporal lobe and the rolandic area; hence we can probably rule out a cerebral abscess. The next possibility is a subdural abscess which, to a certain extent, was walled off but nevertheless was spreading. The initial chill argues for the spread of infection from the frontal sinus either by direct extension from a necrosed posterior wall or through some venous channel. The onset and progression of the hemiplegia argue for spreading of the process in this region. The spinal-fluid findings argue against any general infection of the cerebrospinal fluid and again point to a localized process in the rolandic area. So I think the diagnosis probably should be a subdural abscess with a certain amount of cerebritis in the rolandic area and possibly a phlebitis or thrombosis of the longitudinal sinus.

Dr. Charles I. Johnson: I saw this patient and believed that the intracranial infection started from the sinuses, although there was not a great deal of x-ray evidence of sinusitis. I thought that the infection was extending so rapidly that any operation was not to be considered and that the only chance the man had, which was negligible, lay in the direction of chemotherapy.

Clinical Diagnoses

Basilar meningitis.
Pansinusitis.
Brain abscess?

Dr. Tobey's Diagnoses

Acute exacerbation of chronic sinusitis.
Subdural abscess, left temporal region.
Cerebritis.
Thrombosis of longitudinal sinus?

Anatomical Diagnoses

Subdural abscess.
Sinusitis, acute and chronic, left antrum, frontal sinus and ethmoid, with extension from the last to the subdural space and left orbit.
Communications between sinuses and socket of extracted tooth.

Pathological Discussion

Dr. Kubik: At autopsy a subdural abscess was found on the left side. There was pus in the left ethmoid, the left antrum and the left frontal sinus. The left ethmoid was apparently responsible for infection of the orbit and subdural space. Part of the thin bony roof had been destroyed, and the dura over it was necrotic, so that there was a communication between the infected cells and the subdural space. There was also a defect leading from the ethmoid to the orbit. Communications also existed between the left ethmoidal cells and left antrum and between the left antrum and the socket of the extracted tooth. It was therefore possible to demonstrate a passage leading from the tooth socket through the antrum and ethmoid into the orbit and through the dura. The subdural abscess covered approximately the anterior two thirds of the lateral surface of the brain, — the medial and orbital surfaces of the frontal lobe and the inferior surface of the temporal lobe. Beneath the abscess there was a subarachnoid exudate and the surface of the brain was spotted with numerous small ecchymoses. There was neither a generalized nor a basilar meningitis. The venous sinuses appeared to be negative.

Microscopic examination revealed a subdural exudate and, beneath that, a localized subarachnoid exudate and recent ischemic necrosis of the gray matter down to and including the third layer of the cortex. The pathologic lesions in this case provide a good example of what is generally found. Dr. Raymond Adams and I have collected 11 cases examined here in the past four years. Most of these have occurred as a result of chronic sinusitis (usually frontal sinus or ethmoid), two or three as a result of otitis media. Infection may reach the subdural space through the dura, as in this case, or along venous sinuses and veins in which there is thrombophlebitis. The location of the abscess has been the same in each case. Leptomeningitis limited to the parts of the brain beneath the subdural abscess has been a constant

finding and in nearly every case the cerebral cortex has suffered severe, irreparable damage. These are not abscesses in the true sense. The pus fills a preformed space and is not walled off. In the older cases there is some organization of the exudate next to the dura, but this does not surround the collection of pus.

We find on going over the clinical records that the symptoms and findings generally follow a fairly definite pattern, and we believe that the condition can be diagnosed in a larger proportion of cases than it has been in the past. There is the history of chronic sinus infection or, less often, of chronic middle-ear infection, which may have been going on for years. Then, presumably with the beginning of the subdural infection, there is severe headache, usually more severe in the early stages on the affected side. The patient is drowsy and looks very ill. The temperature quickly rises to from 103 to 105°F. or higher. There is rigidity of the neck. The spinal fluid, which is nearly always under increased pressure (ranging from 190 to 350 mm. of water), contains both lymphocytes and polymorphonuclear leukocytes (15 to 1000 per cubic millimeter) and an elevated total protein. The sugar and chlorides are normal and so help to differentiate this condition and a generalized leptomeningitis. Stupor increases and toward the last, usually with the onset of deep coma, focal signs appear. The important ones most frequently found are one or more of the following: hemiparesis, hemiplegia, paralysis of contralateral conjugate deviation of the eyes and, in left-sided lesions, aphasia. In most of the cases complicating nasal-sinus infection, another very important early sign is swelling about the eye on the affected side. The course is extremely rapid, and death occurs in from five to fifteen days.

The outstanding features which should lead one to suspect subdural abscess are swelling about the eye (in cases with nasal-sinus infection), severe lateralized headache, high fever, drowsiness rapidly progressing to stupor, and rigidity of the neck associated with a low or moderately increased cell count in a spinal fluid under elevated pressure in which the sugar and chlorides are normal. With the onset of focal signs one can be reasonably sure of the diagnosis, but by that time the outlook is all but hopeless. It might be possible to save some of these patients if the abscess could be drained before these events develop, or perhaps even at the beginning of this stage. With the help of chemotherapy the outlook ought to be better than it has been in the past. I believe, too, that valuable time should not be lost in operations on sinuses, osteomyelitis of the frontal bone, mastoids and so forth. These conditions can be dealt with later if the patient recovers after drainage of the abscess.

DR. TOBEY: Was there any generalized meningitis?

DR. KUBIK: The subarachnoid exudate was quite well limited to the area which was covered by the abscess. That is the usual finding, and in most of these cases there is practically no basilar meningitis.

DR. TOBEY: The tooth extraction probably precipitated the whole thing.

DR. RACKEMANN: How do you explain the increased cells in the spinal fluid?

DR. KUBIK: By the localized meningitis beneath the subdural abscess.

CASE 26352

PRESENTATION OF CASE

A fifty-five-year-old American Negro painter entered complaining of shortness of breath, diarrhea and vomiting.

Approximately one year before entry the patient had had a slight cold, following which he began to have shortness of breath and a slight cough productive of yellowish-white sputum. The ankles became swollen toward evening and improved overnight, although the right foot remained slightly swollen all the time. Seven months before entry he noted that he became fatigued very easily and had palpitation. Three months before admission he began to have watery diarrhea two or three times a day for a few days a week. He also vomited occasionally after meals. Neither the vomitus nor the stools contained blood. At this time his urine was "muddy." The face became swollen occasionally. One week before entry he took some "salts," with moderate relief of the vomiting. The urinary output had decreased, and he had become thirsty. Two days before entry he was somewhat dizzy, his vision was blurred and everything appeared hazy. He had had no chest pain or fever. He had had nocturia once a night for the past four years.

The family and marital histories were noncontributory.

Three and a half years before entry he was in this hospital, at which time a bilateral vasectomy and suprapubic cystotomy were performed for an obstructing prostate. At that admission the heart was not enlarged. The blood pressure was 138 systolic, 90 diastolic; the peripheral arteries were sclerosed. There was bilateral exophthalmos. The urine showed a slight trace of albumin and had specific gravities of 1.018 and 1.040. The non-

protein nitrogen ranged between 54 and 88 mg. per 100 cc.; a renal function test showed 13 per cent excretion of the dye in two hours. One month later he was readmitted to this hospital. A consultant found no cardiac symptoms but considerable edema of the feet. The heart was not enlarged, and no murmurs were heard. The blood pressure on admission was 168 systolic, 110 diastolic. The nonprotein nitrogen of the blood was 48 mg. per 100 cc., and the renal function test showed 20 per cent excretion in two hours. The urine had a specific gravity of 1.020. He was given digitalis preoperatively. A suprapubic prostatectomy was performed. The pathological report was: "Benign hypertrophy and chronic prostatitis."

Physical examination showed a well-developed and well-nourished man, lying in bed in no apparent discomfort. The breath had a uriniferous odor. The face and eyelids were puffy. The mucous membranes were pale. The eyes showed exophthalmos, more marked on the right, and myopia. Light perception was present only in the right eye. Both lenses showed opacities. There was marked bilateral chorioretinitis, with retinal atrophy and pigment changes. Inguinal lymph nodes were felt on both sides. Both lungs showed a few moist rales at the bases, with scattered inspiratory and expiratory rhonchi; the breath sounds were rough throughout both lungs. The heart was slightly enlarged to the left, the maximal apical impulse being felt 10.5 cm. from the mid-sternal line in the fifth interspace, 1.0 centimeter beyond the mid-clavicular line. The sounds were of good quality. There was a soft blowing systolic murmur at the apex. The aortic second sound was slightly accentuated. The blood pressure was 178 systolic, 122 diastolic. The peripheral arteries were firm and palpable. There was moderate pitting edema of both feet, ankles and lower legs.

The temperature was 98°F., the pulse 95, and the respirations 22.

Examination of the urine showed specific gravities ranging from 1.008 to 1.015, a large trace of albumin and 10 to 20 white blood cells and 3 to 4 red blood cells per high-power field. The blood showed a red-cell count of 2,700,000 with a hemoglobin of 50 per cent, and a white-cell count of 6700 with 68 per cent polymorphonuclears. A blood Hinton test was negative. The nonprotein nitrogen of the blood was 102 mg. per 100 cc., the carbon dioxide combining power 51.6 vol. per cent, and the serum protein 5.6 gm. per 100 cc.; the chlorides were equivalent to 101 cc. of N/10 sodium chloride. The renal function test showed 0 per cent excretion at the end of an hour and fifteen minutes. The stools were negative.

On the second day he had an attack of what was called cardiac asthma. He was in bed when suddenly his lungs became markedly congested. He developed coarse rhonchi, and the blood pressure rose to 300 systolic, 160 diastolic. Blood-pressure cuffs were applied to the four extremities, with a pressure of 200 mm. of mercury. This produced relief within seven minutes. The patient stated that it was the first attack of this kind that he had ever had. On the third day an apical protodiastolic gallop rhythm was heard. The chest was filled with coarse asthmatic rales, as well as with small fine ones. During the day he had several attacks similar to that on the day before, all relieved by the application of blood-pressure cuffs. He continued to have these attacks and died on the fifth day in an attack of acute pulmonary edema.

Differential Diagnosis

Dr. Robert E. Glendy: It is apparent from the antecedent history that three and a half years before his final admission to the hospital this man had had uremia as a result of urinary suppression from prostatic disease, which, according to the pathological report following prostatectomy, was attributable to benign hypertrophy and chronic prostatitis. There was evidence of considerable impairment of renal function, including albuminuria, poor excretion of dye and nitrogen retention in the blood. The blood pressure was high (168 systolic, 110 diastolic) before prostatectomy. In view of the hypertension it is fair to assume that he had had chronic prostatic obstruction over a rather prolonged period before seeking relief. It is very likely also that because of back pressure due to the obstructing prostate the kidneys were permanently dilated and irreparable damage had been done to the renal parenchyma (atrophy and perhaps some infection). The elevated blood pressure, no doubt present for some time before prostatectomy, must have resulted in a certain amount of cardiac strain, but no cardiac enlargement or other evidence of cardiac disability was recorded at this time, although he was given digitalis preoperatively, perhaps as a precautionary measure. The marked edema of the feet was probably renal in origin from retention of water and salts and possibly a low serum protein. The peripheral arteries were said to be sclerosed, but this fact does not necessarily bear any direct relation to the condition of the arteries elsewhere, since mild to moderate degrees of peripheral arteriosclerosis are not uncommon at this age. Bilateral exophthalmos was observed at both hos-

pital admissions but presumably was not related to the illnesses described here.

The past medical history reveals that he had had erysipelas in early life. One might speculate about the possibility of a complicating nephritis with some early renal impairment, but this is such a far cry that it hardly deserves mention. Because of the exposure to lead as a painter I wonder about chronic lead poisoning as a possible factor, at least in the production of the degenerative changes — arteriosclerosis and interstitial nephritis with hypertension — that are so often present in the late stages of this condition. In the absence of other manifestations of lead poisoning we can go no farther than to consider it as a possible contributing factor. The history of pleurisy at the age of twenty-one does not seem to fit into this picture anywhere.

Except for the statement that he had had nocturia we have no information about the state of his health for some two and a half years following the prostatectomy. Then one year before entry the signs and symptoms of his final illness began. They were ushered in by a cold, which not uncommonly precipitates or aggravates cardiovascular symptoms. The dyspnea, cough and swelling of the ankles noted toward evening undoubtedly represent the end result of long-standing myocardial strain from arterial hypertension, manifesting itself in a diminished cardiac reserve with some gross evidences of failure. These symptoms increased as time went on, and to them were added others, namely, easy fatigue and palpitation. The diarrhea, vomiting, decrease in urinary output, swelling of the face, dizziness and disturbance in vision that developed during the three months prior to entry all point to advancing renal failure which, I believe, is the underlying factor behind the whole picture. The "muddy" urine might be expected with the decreased urinary output, and also suggests that there was some infection in the urinary tract. The absence of fever, however, is against an acute infection, at least one of much importance. The mechanism behind the gastrointestinal symptoms may have been local edema of the viscera or uremic toxemia or both. Finally, the dizziness and disturbance of vision suggest cerebral edema and vascular lesions in the optic fundi, respectively.

These assumptions from the history find confirmation in the physical findings. The uriniferous breath, puffy face and eyelids, pallor of the mucous membranes, retinal changes, hypertension, cardiac enlargement, pulmonary congestion and peripheral edema are altogether typical of cardiorenal disease. I presume that the changes in the optic fundi were described as chorioretinitis simply because the choroid was prominently implicated. The myopia may have contributed to this, but with retinal atrophy the choroidal vessels naturally become more easily visible. Opacities of the lenses were additional factors in his failing vision. The systolic murmur at the cardiac apex was probably due to dilatation of the left ventricle, with functional mitral regurgitation.

The laboratory studies showed a urine containing a large amount of albumin and cellular elements consistent with both chronic nephritis and some mild infection anywhere along the urinary tract. Casts were conspicuous by their absence. This seemed to merit more than passing consideration, so I asked that this be confirmed before going farther with the case, and I was assured that no casts were present. Assuming this to be an accurate observation we therefore have some evidence to support the idea that the renal failure resulted from the earlier effects of prostatic obstruction plus some chronic infection rather than from nephritis of non-surgical origin. The absence of casts is rather the rule than the exception in surgical nephritis. The ability of the kidneys even at that late date to concentrate the urine to 1.015 also favors surgical nephritis, in which the remaining functioning cells undergo compensatory changes in size and function that are not encountered in other types of nephritis. The anemia, nitrogen retention and lowered serum protein are all consistent with the picture of renal failure, which is quite apparent also from the inability of the kidneys to excrete the dye used in the renal-function test. The carbon dioxide combining power of the blood was at the lower limit of normal. With such marked impairment of kidney function one would expect it to be lower.

From the account of the last few days of his life it is apparent that he died of myocardial failure, when his heart could no longer compensate for the strain imposed upon it by the marked elevation of blood pressure. This, I believe, was secondary to the underlying renal disease.

In summarizing the whole situation the sequence of events seems to have been prostatic obstruction with back pressure, infection, and more or less permanent damage to the renal parenchyma with some temporary relief following prostatectomy. The renal damage was probably perpetuated by chronic infection. Hypertension and cardiac hypertrophy subsequently became a prominent part of the picture as the renal impairment advanced, and he finally succumbed to renal and cardiac failure.

My prediction is that the kidneys showed pro-

nounced atrophic changes in the parenchyma, along with arteriolar and capillary changes of a diffuse nature. The kidney pelves and calyces may have shown evidence of the old prostatic obstruction. Judging from the urinary findings, blood counts and temperature there was probably not much evidence of recent purulent infection in the urinary tract, although infection undoubtedly contributed to the impairment of renal function over the period of years. The heart was undoubtedly dilated and hypertrophied, with preponderant enlargement of the left ventricle, and the lungs waterlogged.

Clinical Diagnoses

Chronic glomerular nephritis, with hypertension and hypertensive heart disease.
Uremia.
Cardiac asthma.

Dr. Glendy's Diagnoses

Chronic pyelonephritis, with atrophic and inflammatory, arteriolar and capillary lesions.
Hydronephrosis.
Hypertensive heart disease.
Marked cardiac enlargement.
Congestive heart failure.
Pulmonary edema.

Anatomical Diagnoses

Pyelonephritic atrophy of the kidneys (healed pyelonephritis).
Hypertrophy of the heart.
Pulmonary edema.
Chronic passive congestion, slight.
Arteriosclerosis, cerebral.
Operative wound: suprapubic prostatectomy.

Pathological Discussion

Dr. Tracy B. Mallory: As Dr. Glendy predicted, this patient showed atrophic kidneys, a hypertrophied heart and wet edematous lungs. The systemic arterial system, including the coronary arteries, showed remarkably little arteriosclerosis, but the small arteries and arterioles of the brain were, in contrast, rather markedly involved. The interest of the anatomical diagnoses lies in the nature of the renal lesion. There was no gross dilatation of the renal pelves, and the renal cortices were diffusely rather than focally scarred, so that a gross diagnosis of pyelonephritis was not suggested. On microscopic examination, however, several findings which have recently been emphasized by Weiss and Parker* point to a pyelonephritic atrophy. There are great numbers of completely hyalinized glomerular tufts, with unusually marked periglomerular fibrosis. There is disproportionate tubular destruction, and definite increase of interstitial fibrous tissue, with considerable lymphocytic infiltration but no evidence of acute infection. Many of the tubules contain the dense so-called "colloid" casts. The blood vessels show very marked intimal proliferation. The histological criteria, therefore, appear to substantiate completely Dr. Glendy's diagnoses.

*Weiss, S., and Parker, F., Jr.: Pyelonephritis: its relation to vascular lesions and to arterial hypertension. *Medicine* **18**:221-315, 1939.

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MEDICAL PREPAREDNESS: INDUSTRIAL MEDICINE

As already stated editorially, an unexcelled efficiency of machines is but of little advantage to preparedness if the production of war supplies is hampered by a physical breakdown of those who man them. Hence, any scheme to further national defense should include elaborate plans for the protection of the worker and his family.

The broader aspects of the problem have to do with the health of the nation as a whole, and as previously noted, include an improved nutritional status, the correction of remediable defects and the application of approved procedures of preventive medicine. But the protection of the skilled worker, — of whom there is acknowledged to be a serious shortage, — as well as that of apprentices who are now employed or who may eventually replace those called into active service, demands the intelligent application of present-day knowledge concerning industrial medicine. This is particularly true in those industries that are forced to expand by leaps and bounds: new hazards are sure to occur, and there is certain to be relatively less protection against those that have long been recognized. Adequate preventive measures must be instituted, and those who are injured or become ill while employed must receive the best of medical and nursing care.

In the past twenty-five years, the art and science of industrial medicine have rapidly advanced, largely through the impetus afforded by private industry, when, as the handicap caused by the loss of working time by indispensable workers began to be appreciated, it took steps to protect the health of its employees. This branch of medicine is now a well-recognized and well-justified specialty, and more and more physicians have become interested in it, on either a part-time or full-time basis. Instruction can be obtained in certain medical schools or schools of public health, and federal and state agencies are maintained to assist in solving whatever problems arise. The Council on Industrial Health of the American Medical Association has recently become quite active, and through its efforts, committees on industrial health have been organized among the state medical societies within the past two years. All these facilities are available, but they must be augmented if the challenge offered by potentially tremendous industrial expansion is to be properly met. An increase in trained personnel is needed, and the Committee on Medical Preparedness of the American Medical Association has recently recommended to the National Defense Commission "that the necessary funds be furnished to the U. S. Public Health Service to provide the training of physicians, chemists, mechanical engineers and other professional personnel in order to cope with the industrial hygiene problem in the present national emergency."

FIVE-DAY TREATMENT OF SYPHILIS

Ehrlich's vision of a one-dose method of treating syphilis has been revived. At a recent conference in New York City a report[1] was made of the so-called "five-day treatment of syphilis," using arsphenamine preparations highly diluted in

salt solution and introduced into a vein at a rate of thirty drops a minute for a period of hours on successive days. The results obtained warrant further experiment with the method, which was devised in 1933 by Chargin, Leifer and Hyman.[2] Twenty-five patients were treated at that time, but only 13 of them have been followed up and found to be serologically and clinically negative. In the more recent series, 86 patients were treated with neoarsphenamine and 300 with a new drug called phenylarsine oxide. There are apparently fewer toxic reactions with the latter drug, but the time has been altogether too short to render an opinion on its efficacy. Thus far only one type of patient has been treated — selected healthy men with primary syphilis. Much work is necessary before this method should be widely used.

A recent review[3] summarizes well the limitations of this new method and the cautions to be observed. More cases that have been treated in this way and observed over a long period are needed before a correct estimate of its value can be made. It is possible that other drugs of the arsphenamine series, either alone or combined with a course of bismuth or another heavy metal, and perhaps repeated later, may prove more satisfactory; furthermore, the dosage and time element should be varied in order to obtain the best combination. The patients must be carefully selected, the investigations must be performed in large medical centers with skilled personnel, and a careful evaluation of the results must be made. This new procedure offers the possibility of a more rapid control of syphilis by stopping the infection in a relatively short period of time, but the perfection of the method will take time. While awaiting these developments it should be remembered that very satisfactory results are being obtained with the present standard treatment and that cases of syphilis should be treated strictly by this method until the newer one has been proved to be superior in its end results.

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2. Chargin, L.; Leifer, W., and Hyman, H. T.: Studies of velocity and the response to intravenous injections. V. The application of the intravenous drip method to chemotherapy as illustrated by massive doses of arsphenamine in the treatment of early syphilis. *J. A. M. A.* **104:**878-883, 1935.
3. Clarke, C. W.: The five-day treatment for syphilis. *J. Soc. Hyg.* **26:**212-216, 1940.

MEDICAL EPONYM

Credé's Maneuver

This obstetric maneuver for expression of the placenta was devised by Carl Siegmund Franz Credé (1819–1892), while he was director of obstetrics and gynecology at the Charité in 1846–1848. The procedure was mentioned in his *Klinische Vorträge über Geburtshülfe* [Clinical Lectures on Obstetrics] (Berlin: August Hirschwald, 1853), but his first exact description was presented before the gynecologic section of the congress of German physicians held in Königsberg in 1860. This is reported in the *Monatsschrift für Geburtskunde* (**16:** 338, 1860). A portion of the translation follows:

> The whole hand is first gently laid over the region of the uterus, and gentle stroking motions are made over as large a portion of the uterine surface as possible until the beginning contraction is perceived beneath the hand; then the uterus is grasped by the hand with fingers spread, or if one hand does not suffice, with both hands, and the moment the contraction seems to have reached its greatest strength, downward pressure is boldly exerted on the fundus and walls of the uterus in the direction of the pelvic outlet. Thereupon, the whole placenta and the blood which may have collected behind it are rapidly expelled.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

SECTION OF OBSTETRICS AND GYNECOLOGY*

Raymond S. Titus, M.D., *Secretary*
330 Dartmouth Street
Boston

Lobar Pneumonia in the Eighth Month of Pregnancy

Mrs. M. C., a thirty-two-year-old para III in the eighth month of pregnancy, while at the theater on April 3, 1940, had a sudden chill with pain in the upper left chest and felt sick and weak. She was referred immediately to the hospital.

The family history was non-contributory. The patient's past history included the usual children's diseases. A suspension of the uterus had been performed in 1937. The two previous pregnancies had been normal and uneventful throughout. Catamenia began at twelve, were regular with a twenty-eight-day cycle and lasted four days. The last menstrual period began on August 4,

*A series of selected case histories by members of the section will be published weekly. Comments and questions by subscribers are solicited and will be discussed by members of the section.

1939, making the expected date of confinement May 11.

The patient was first examined in the office on September 29, 1939, at which time all physical findings were normal and the uterus was definitely enlarged, with slight softening of the anterior wall. The pregnancy was uneventful except for a slight cold and cough for one week before hospital entry.

Within one to two hours after admission to the hospital she developed a severe hacking cough, which was painful, and raised some sputum, which was slightly bloody. As she presented the typical picture of an acute lobar pneumonia, she was seen by an internist. The temperature was 102°F., the pulse 120, and the respirations 25. The left chest was splinted; motion, cough and deep breathing were all painful, and the pain was referred largely to the region of the left clavicle. Examination revealed the throat red and dry, the tongue slightly coated. There were no palpable lymph nodes. The lungs showed decreased resonance and breathing over the whole left chest, particularly posteriorly, and a friction rub in the left axilla. There were no definite rales or changes in breathing. The right lung was clear throughout. The heart sounds were rapid but otherwise normal. The abdomen was increased in size to that of an eight months' pregnancy. There was no costovertebral tenderness. A diagnosis of lobar pneumonia, probably in the left lower lobe, was made. As there was no portable x-ray equipment available, no films were taken. A typing, reported less than nine hours after the onset of the disease, showed Type 7 pneumococcus. In view of the fact that the patient was known to be allergic, serum was not given and sulfapyridine was started — 30 gr. immediately, 30 gr. in two hours, and then 15 gr. every four hours. She was given 1/6 gr. of morphine subcutaneously, and a chest swathe was applied. The hemoglobin was 84 per cent (Sahli), the red-cell count 4,050,000, and the white-cell count 25,100. A blood culture taken before the medication was started showed a Type 7 pneumococcus.

In twelve hours the temperature had dropped to 100°F., but the patient was still somewhat toxic. The signs in the chest were fairly well localized in the left base, with dullness in the axilla and a little posteriorly. There were a few crackling rales over this area, with the friction rub still present but less marked. The patient was nauseated from the sulfapyridine.

On April 5 she began to look much better. The signs in the lungs started to clear, and the breath sounds came through better, being slightly bronchial. The rales were more noticeable in the upper part of the left lobe. Sulfapyridine was then given every six hours. The hemoglobin had dropped to 66 per cent (Sahli), and the red-cell count to 3,430,000. From this time on, the patient made rapid progress and the lungs cleared rapidly. She was moved by ambulance to another hospital, where more satisfactory nursing care could be arranged. Ten days after the onset of the infection, x-ray films showed the lungs to be clear, and the patient was discharged home on the twelfth day.

Two weeks later, the patient started in labor and was delivered of a normal male child. She remained in the hospital for sixteen days and had a normal puerperium.

Comment. This case illustrates proper treatment and an ideal result. Chemotherapy appears to be as effective in cases of pneumonia in pregnancy as it is in uncomplicated pneumonia, and early hospitalization, early consultation, early typing and early chemotherapy may reduce the mortality of pneumonia during pregnancy to such a level that its inherited fear will be dispelled.

DEATHS

JENKINS — Thomas L. Jenkins, M.D., of Topsfield, died July 29. He was in his seventy-fifth year.

Dr. Jenkins received his degree from Harvard Medical School in 1890 and was a fellow of the Massachusetts Medical Society and the American Medical Association. During the World War he was a senior surgical officer of the American Expeditionary Force.

THORNDIKE — Augustus Thorndike, M.D., of Boston, died August 23. He was in his seventy-eighth year.

Born in Paris, France, he attended Noble's School in Boston and Harvard College. He received his degree from the Harvard Medical School in 1888 and served as house officer and intern at the House of the Good Samaritan, the Massachusetts General Hospital and the Boston Lying-in Hospital. Dr. Thorndike was associated with the Boston Dispensary until 1895, serving consecutively as assistant district physician, orthopedic surgeon and surgeon. He had also served as visiting physician at St. Luke's Home for Convalescents and the House of the Good Samaritan and assistant surgeon at the Children's Hospital in Boston. From 1907 to 1917 he was a member of the Department of Orthopedic Surgery at the Harvard Medical School.

He was a member of the Massachusetts Medical Society and the American Medical Association and a fellow of the American College of Surgeons. He also held memberships in the Massachusetts Medical Benevolent Society, Boston Society of Medical Sciences, and Boston Medical Library.

His sons, Dr. Augustus Thorndike, Jr., Robert and Charles, and his daughters, Alice and Mary, survive him.

CORRESPONDENCE

LICENSING OF ALIEN PHYSICIANS

To the Editor: I have just finished reading the editorial, "Aliens and the Practice of Medicine." When I took the state examinations last November I was struck by the number of refugees in the examination rooms. They were of all ages, varying from a quiet, elderly man, who evidently had been a teacher in his native land, judging from the number of young people who clustered around him between examinations, to a young girl, who became hysterical on observing one of the examinations.

Rather than judging this hodge-podge *en masse* I believe it would be better to individualize treatment. Let the president of the Massachusetts Medical Society appoint a committee to examine them and their credentials, so as to make recommendations to the Board of Registration in Medicine as to whether they would be better fitted to (a) study longer in an American medical school, (b) intern for a year in an American hospital, (c) take the examinations for practice or (d) be admitted to practice without examination, presumably to continue a specialty or become a teacher in a medical school.

I think such a plan as this would protect the public from incapable practitioners and would not place the refugee in a position untenable to him. By doing this the medical profession will assume a responsible position in this problem.

JOSEPH A. BRADLEY, M.D.

215 Haverhill Street,
Lawrence, Massachusetts.

* * *

By statute the licensing of physicians is a function of the Board of Registration in Medicine, and the procedure employed in determining the fitness of candidates is also defined by law. While Dr. Bradley's suggestion is reasonable, the participation of the Massachusetts Medical Society in determining the qualifications of candidates would necessitate additional legislative action. ED.

REPORTS OF MEETINGS

BOYLSTON MEDICAL SOCIETY

At the Harvard Medical School on May 5, the Boylston Medical Society presented Professor Charles H. Best, of the University of Toronto, who spoke on "Factors Influencing the Production and Liberation of Insulin from the Pancreas."

The effects of various diets and of starvation on the insulin content were first considered. The smallest amounts of insulin were extracted from rats either starved or fed solely on fat. These animals showed a glucose-tolerance curve simulating a diabetic curve, which indicates that the rate of release of insulin, as well as the total amount, is diminished under these dietary conditions. Microscopic examination of the islet cells in such animals, however, failed to reveal any notable changes indicative of degeneration. Finally, it was noted that recovery from this depressed state of insulin production was best accomplished by a balanced diet. Rats fed on high-fat diets showed smaller quantities of insulin than did similar animals on an equicaloric carbohydrate diet. Prolonged experiments on high-carbohydrate and fat diets failed to show such striking variations from normal.

Newer investigations on the effect of insulin on normal as well as on fat-fed and starved rats reveal that the use of this hormone further depresses the production of insulin from the pancreas and suggest that all these procedures are measures to cause a reversible "atrophy of disuse" in the islet cells. The apparent diabetic glucose-tolerance curve, therefore, is really an indication of a resting state, which is evidenced by the gradual resumption of the usual production when the normal diet without insulin is initiated. This finding was held to elucidate the diabetic-tolerance curve observed in tumors of the islet cells which oversecrete hormone and consequently depress production by normal tissue, which then responds only sluggishly, if at all, to carbohydrate stimulation. It also explains the findings in the insulin treatment of dementia praecox.

In order to investigate the effect of the diabetogenic extract of the anterior pituitary gland, as used by Houssay to produce transient, and by Young to produce permanent diabetes, Best and his collaborators removed the pancreas of animals treated by the Young method and found no increase in the intensity of the disease. Young had reported changes in the pancreas, and Best and his collaborators found a decrease of insulin content. It was suggested, therefore, that the pancreas is the intermediary whereby the hypophysis exerts its effect. Furthermore, the islet cells reveal no evidence of recovery in permanent pituitary diabetes in the dog.

Preliminary results of some recent studies demonstrate that the administration of insulin prevents the production of permanent pituitary diabetes in susceptible animals, that no degenerative changes, except proliferation, were brought about in the pancreas, and that no marked diminution of insulin content occurred.

Dr. Best concluded that starvation, a fat diet or the administration of insulin rests the islet cells and protects them from the effects of the diabetogenic hormone of the anterior pituitary gland. Possible clinical application of these facts was suggested in order to rest the islet cells from the possible deleterious effects of the pituitary gland in a susceptible person. A diet low in calories, low in carbohydrate or high in fat, with or without the addition of insulin, may be prescribed. If stimulation is desired subsequently, a high-carbohydrate diet may be employed, with insulin used for protection. This procedure supports the early views of Allen to the effect that the islet cells are capable of protection by proper diets. A difficult clinical experiment, the observation of 1000 children with a family history of diabetes rested by diet (and insulin) and 1000 controlled cases for the incidence of subsequent diabetes, was suggested.

ALPHA OMEGA ALPHA

At the Harvard Medical School on May 15, the Harvard Chapter of Alpha Omega Alpha presented Professor Robley Evans, of the Massachusetts Institute of Technology, who spoke on "Some Medical Applications of Radioactivity."

A review of the physical aspects of radioactivity was given; and the statement was made that any competent cyclotron today is capable of producing more radioactivity than all the radium in the world. Every known chemical substance has now been transmuted by this method. Dr. Evans pointed out that artificial radioactive compounds are actually "spies" rather than "tracers," for they are indistinguishable from the natural element in ordinary mixtures.

In indicating some of the applications of radioactivity to medicine, Dr. Evans ranked it in importance with the microscope and roentgen rays. One use of radioactivity has been in the study of iodine metabolism carried on by

the combined physician-physicist team of Drs. Means, Hertz, Roberts and Evans. It has revealed that this element, and not all halogens, are selectively concentrated by the thyroid gland. The greatest collection of circulating iodine occurs in the first ten to fifteen minutes. It is especially marked in pregnancy and hyperplasia of any sort. In fact the iodine accumulation by the thyroid gland is seventy times that expected if a general diffusion had taken place. Hyperplasia from cyanide and cabbage ingestion in rabbits causes a differently shaped, although grossly similar, curve of accumulation. Due to the fact that the greatest amount of iodine is concentrated in the thyroid gland after the first dose of iodine, it was considered possible that a single dose of potassium iodide might serve as well as repeated ones in the treatment of hyperplastic thyroid disease in man. Preliminary reports on this work indicate that this is actually the case, at least in certain persons.

NOTICES

ANNOUNCEMENT

JOHN J. SLATTERY, M.D., announces the removal of his office, effective September 1, 1940, from 95 to 89 Mt. Auburn Street, Watertown.

NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly staff meeting of the New England Hospital for Women and Children will be held in the classroom of the nurses' residence on Thursday, September 5, at 7:15 p.m. The subject will be "Clinicopathological Reports on Two Cases with Pancreatic Disease." Dr. Gulli Lindh Muller will preside.

SOCIETY MEETINGS AND CONFERENCES

SEPTEMBER 2–6 — American Congress of Physical Therapy. Page 862, issue of May 16.

SEPTEMBER 5 — New England Hospital for Women and Children. Notice above.

SEPTEMBER 12–MAY 8 — Pentucket Association of Physicians. Page 263, issue of August 15.

SEPTEMBER 16 — New England Society of Anesthesiology. Page 305, issue of August 22.

SEPTEMBER 16–20 — American Occupational Therapy Association. Page 263, issue of August 15.

SEPTEMBER 17–19 — Clinical Congress of the Connecticut State Medical Society. Page 305, issue of August 22.

OCTOBER 6–11 — Annual meeting of the American Academy of Ophthalmology and Otolaryngology. Page 81, issue of July 11.

OCTOBER 8–11 — American Public Health Association. Page 655, issue of April 11.

OCTOBER 11, 12 — Pan-American Congress of Ophthalmology. Page 898, issue of May 23.

OCTOBER 14–25 — 1940 Graduate Fortnight of the New York Academy of Medicine. Page 305, issue of August 22.

OCTOBER 21 — American Board of Internal Medicine. Page 369, issue of February 29.

JANUARY 4, 1941 — American Board of Obstetrics and Gynecology. Page 1064, issue of June 20.

MARCH 8 — American Board of Ophthalmology. Page 201, issue of August 1.

APRIL 21–25 — American College of Physicians. Page 1065, issue of June 20.

DISTRICT MEDICAL SOCIETY

SUFFOLK

NOVEMBER 7 — Censors' meeting. Page 305, issue of August 22.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Synopsis of the Principles of Surgery. By Jacob K. Berman, A.B., M.D., assistant professor of surgery, Indiana University School of Medicine, Indianapolis. 12°, cloth, 615 pp., with 274 illustrations. St. Louis: C. V. Mosby Company, 1940. $5.00.

The Bacteriology of Public Health. By George M. Cameron, Ph.D., associate professor of bacteriology, University of Tennessee. 8°, cloth, 451 pp., with 35 illustrations and 8 color plates. St. Louis: C. V. Mosby Company, 1940. $3.50.

The Emperor's Itch: The legend concerning Napoleon's affliction with scabies. By Reuben Friedman, M.D., assistant professor of dermatology and syphilology, Temple University School of Medicine, Philadelphia. 8°, cloth, 82 pp., with 10 illustrations. New York: Froben Press, 1940. $1.50.

Manual of Medical and Surgical Emergencies. Edited by J. C. Geiger, M.D., director, Department of Public Health, City and County of San Francisco, California. 8°, cloth, 199 pp. San Francisco: J. W. Stacey, Inc. $2.50.

Legal Guide for American Hospitals: Prepared in collaboration with the Council on Government Relations of the American Hospital Association. By Emanuel Hayt, LL.B., and Lillian R. Hayt, M.A., J.D., of the New York Bar. 8°, cloth, 608 pp. New York: Hospital Textbook Company, 1940. $5.00.

American Doctors of Destiny: A collection of historical narratives of the lives of great American physicians and surgeons whose service to the nation and the world has transcended the scope of their profession. By Frank J. Jirka, M.D., with an introduction by Harold W. Camp. 8°, cloth, 361 pp., with 20 portraits by Raymond Warren. Chicago: Normandie House, 1940. $3.75.

Dynamics of Inflammation: An inquiry into the mechanism of infectious processes. By Valy Menkin, M.D., instructor, Department of Pathology, Harvard Medical School. 8°, cloth, 244 pp., with 50 illustrations and 27 tables. New York: Macmillan Company, 1940. $4.50.

Observations Made during the Epidemic of Measles on the Faroe Islands in the Year 1846. By Peter Ludwig Panum, M.D., and translated from the Danish by Ada Sommerville Hatcher, with a biographical memoir by Julius Jacob Petersen, M.D., translated from the Danish by Joseph Dimont, and an introduction by James Angus Doull, M.D. 8°, cloth, 111 pp. New York: Delta Omega Society (distributed by the American Public Health Association), 1940. $2.50.

La maladie de Besnier–Boeck–Schaumann: ses manifestations cutanées, ganglionnaires, pulmonaires, osseuses, oculaires, glandulaires, viscérales, nasales, nerveuses — une nouvelle grande réticulo-endothéliose. By L. M. Pautrier, clinical professor of dermatology and syphilology, Faculty of Medicine, Strasbourg. 4°, paper, 341 pp., with 105 illustrations. Paris: Masson et Cie. $2.05.

The International Medical Annual: A year book of treatment and practitioner's index (1940). Edited by H. Letheby Tidy, M.A., M.D. (Oxon.), F.R.C.P., and A. Rendle Short, M.D., B.S., B.Sc., F.R.C.S. 8°, cloth, 545 pp.,

with 65 plates. Baltimore: Williams & Wilkins Company, 1940. $6.00.

Influence of a Public Health Program on a Rural Community: Fifteen years in Rutherford County, Tennessee, 1924-1938. By W. Frank Walker, Dr.P.H., and Carolina R. Randolph. 12°, paper, 106 pp., with 46 tables and 6 charts. New York: The Commonwealth Fund, 1940. 25 cents.

As I Remember Him: The biography of R.S. By Hans Zinsser, M.D., S.D. 8°, cloth, 443 pp. Boston: Little, Brown & Company, 1940. $2.75.

Frank Howard Lahey: Birthday volume (June 1, 1940). 8°, cloth, 466 pp., with 71 illustrations and 29 tables. Springfield, Illinois: Charles C Thomas, 1940. Privately printed.

BOOK REVIEWS

Treatment of War Wounds and Fractures. By J. Trueta, M.D. 12°, cloth, 146 pp., with 48 illustrations. New York: Paul B. Hoeber, Inc., 1940. $2.50.

The author of this volume took a very active part in caring for military and civilian casualties of the late Spanish civil war. From this large experience he concludes that the closed method is by all odds the best treatment for compound fractures. In the United States this therapy has found its widest use in chronic osteomyelitis under the name of "Orr treatment." It consists essentially of thorough debridement, packing of the wound, reduction of the fracture and application of an unpadded plaster cast without a window. When soft-tissue damage is slight, as with a small bullet wound, the packing may be omitted. The early use of this treatment in compound fractures lowers the incidence of serious sepsis, hastens healing and facilitates transportation to hospitals far from the scene of the first treatment.

Of 1073 cases treated by this method, 976 showed good or satisfactory results; there were only 6 deaths. Trueta does not give exact figures for non-union, but he leaves the reader to understand that the number is smaller than that with other methods of treatment.

The problems of individual fractures in both extremities are enumerated, and many representative cases are discussed. There are good illustrations and photographs of the cases. This work has received much favorable attention and deservedly so, for it should help to reduce the mortality and morbidity of these common injuries both in war and in peace.

The Medical Career and Other Papers. By Harvey Cushing. 8°, cloth, 302 pp. Boston: Little, Brown & Company, 1940. $2.50.

In 1928, Dr. Cushing published a group of his papers in a book entitled *Consecratio Medici and Other Papers* (Boston: Little, Brown & Company). Toward the end of his life, he assembled another series of papers on general medical topics, which he had arranged to be published in book form. Since his death in 1939, this task has been carried out by his official biographer, Professor John F. Fulton, of Yale University School of Medicine. The volume contains the reprinting of seven important papers, with the addition of nine biographical sketches. To all readers of the *Journal,* these works of Dr. Cushing are undoubtedly familiar. Some were read in Boston, and many were printed in the *Journal.* It is pleasant to reread them, however, in their present form, and one finds a delightful sense of satisfaction in again visualizing the principles so skillfully depicted by Dr. Cushing's classic pen. No one in recent years has been able to draw such succinct sketches of his contemporaries, nor write with such great brilliance as well as lucidity of style about the old figures of medicine in the past. Moreover, as a reviewer of medicine, particularly as it applied to his own specialty of neurosurgery, Dr. Cushing had no peer. *The Medical Career* is a welcome addition to modern literature; it should be widely read and reread by the present generation and by those to come.

Fundamentals of Biochemistry. By T. R. Parsons, B.Sc., M.A. Sixth ed. 12°, cloth, 461 pp. Baltimore: William Wood & Company, 1939. $3.00.

Because it does not fulfill the requirements of present-day biochemistry and because it is filled with inaccuracies, the sixth edition of this book is a characterless one. The author himself summarizes this fault in his foreword wherein he states: "It has been my desire that any merit my book may possess may result from its containing less of information rather than more than other books contain. . . . But I am fully aware that my anxiety for the omission of detail must have run to such excess as to constitute a fault rather than a virtue." Because the mental connecting rods have been left out in explaining certain biochemical processes, the reader is often perplexed and fails to understand the exact situation. This being the case, the reviewer believes that the book is inadequate for instructive purposes as knowledge depends primarily on understanding rather than memory.

The Rockefeller Institute for Medical Research: Studies from the Rockefeller Institute for Medical Research. Vol. 114. 8°, paper, 640 pp. Baltimore: Waverly Press, 1940. $2.00.

The usual wide range of material is presented. Of special interest is the report of Dubos and others on a bactericidal agent extracted from soil bacteria. The article by Erf and Rhoads on benzol poisoning is of value.

A Handbook of Accepted Remedies, Symptoms and Treatment of Poisoning. Edited by P. J. Hanzlik, M.D. 12°, paper, 127 pp. San Francisco: Department of Public Health, 1940.

In 1936, Dr. J. C. Geiger, director of public health, San Francisco, appointed a committee, consisting of five authorities in the fields of public health and pharmacology, for the purpose of preparing a handbook that would contain facts concerning quantitative data and details of miscellaneous procedure incident to the application to and solution of medical problems.

Beginning with the educational features of this brochure, lists of the approved drugs and methods of treatment of the disorders of the several systems of the human body are presented, and following these, sections dealing with vaccines, serums, bioassays, drugs subject to federal regulation, vitamins, foods, symptoms and treatment of poisoning, common emergencies, physiological and pathological data, diagnostic and other tests and so forth, all are set forth in concise language and logical sequence.

The especial reason for the compilation of these lists of useful agents is because of the accepted fact that few people are endowed with the requisite mental capacity to have immediately available all useful knowledge pertaining to medical problems. Although designed especially for hospital staffs, most practitioners will find it a useful and handy reference book.